

PI: <b>LI, ELLEN</b>	Title: 1/2: Partnership to study racial/ethnic differences in GI cancer biology	
Received: 03/19/2015	FOA: PAR14-152	Council: 10/2015
Competition ID: FORMS-C	FOA Title: FEASIBILITY STUDIES TO BUILD COLLABORATIVE PARTNERSHIPS IN CANCER RESEARCH (P20)	
<b>1 P20 CA192994-01A1</b>	Dual:	Accession Number: 3805676
IPF: 5992612	Organization: STATE UNIVERSITY NEW YORK STONY BROOK	
Former Number:	Department: Medicine	
IRG/SRG: ZCA1 PCRB-C (O1)	AIDS: N	Expedited: N
Subtotal Direct Costs <u>(excludes consortium F&amp;A)</u> Year 1: 150,372 Year 2: 144,131 Year 3: 144,086 Year 4: 144,072 Year 5: 0	Animals: Y Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
<i>Senior/Key Personnel:</i>	<i>Organization:</i>	<i>Role Category:</i>
Ellen Li	The Research Foundation for SUNY, Stony Brook University	PD/PI

## APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&amp;R)

3. DATE RECEIVED BY STATE		State Application Identifier
1. TYPE OF SUBMISSION*		4.a. Federal Identifier CA192994
<input type="radio"/> Pre-application <input checked="" type="radio"/> Application <input type="radio"/> Changed/Corrected Application		b. Agency Routing Number
2. DATE SUBMITTED	Application Identifier	c. Previous Grants.gov Tracking Number
5. APPLICANT INFORMATION <span style="float: right;">Organizational DUNS*: 8048782470000</span>		
Legal Name*: The Research Foundation for SUNY, Stony Brook University		
Department: Office of Sponsored Programs		
Division: OVPR		
Street1*: STONY BROOK UNIVERSITY		
Street2: The Office of Sponsored Programs		
City*: STONY BROOK		
County:		
State*: NY: New York		
Province:		
Country*: USA: UNITED STATES		
ZIP / Postal Code*: 117940000		
Person to be contacted on matters involving this application		
Prefix: Ms.      First Name*: Andria      Middle Name:      Last Name*: Adler      Suffix:		
Position/Title: Grant Administrator		
Street1*: W5510 Melville Library		
Street2: Stony Brook University		
City*: Stony Brook		
County: Suffolk		
State*: NY: New York		
Province:		
Country*: USA: UNITED STATES		
ZIP / Postal Code*: 117943362		
Phone Number*: 631 632-1610      Fax Number: 631 632-6963      Email: andria.adler@stonybrook.edu		
6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)*		1146013200F7
7. TYPE OF APPLICANT*		X: Other (specify)
Other (Specify): Private Non Profit		
Small Business Organization Type <input type="radio"/> Women Owned <input type="radio"/> Socially and Economically Disadvantaged		
8. TYPE OF APPLICATION*		If Revision, mark appropriate box(es).
<input type="radio"/> New <input checked="" type="radio"/> Resubmission		<input type="radio"/> A. Increase Award <input type="radio"/> B. Decrease Award <input type="radio"/> C. Increase Duration
<input type="radio"/> Renewal <input type="radio"/> Continuation <input type="radio"/> Revision		<input type="radio"/> D. Decrease Duration <input type="radio"/> E. Other (specify) :
Is this application being submitted to other agencies?* <input type="radio"/> Yes <input checked="" type="radio"/> No      What other Agencies?		
9. NAME OF FEDERAL AGENCY* National Institutes of Health		10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER 93.398 TITLE: Cancer Research Manpower
11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT* 1/2: Partnership to study racial/ethnic differences in GI cancer biology		
12. PROPOSED PROJECT Start Date*      Ending Date* 09/01/2015      08/31/2019		13. CONGRESSIONAL DISTRICTS OF APPLICANT NY-001

**14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

Prefix: First Name\*: Ellen Middle Name: Last Name\*: Li Suffix:

Position/Title: Chief

Organization Name\*: The Research Foundation for SUNY, Stony Brook University

Department: Medicine

Division: Gastroenterology Hepatology

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Street2: T-17 Room 060

City\*: Stony Brook

County:

State\*: NY: New York

Province:

Country\*: USA: UNITED STATES

ZIP / Postal Code\*: 117948173

Phone Number\*: 631-444-2119 Fax Number: 631-444-8886 Email\*: ellen.li@stonybrook.edu

**15. ESTIMATED PROJECT FUNDING**

a. Total Federal Funds Requested\* \$1,259,624.00

b. Total Non-Federal Funds\* \$0.00

c. Total Federal & Non-Federal Funds\* \$1,259,624.00

d. Estimated Program Income\* \$0.00

**16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?\***

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ☐ PROGRAM IS NOT COVERED BY E.O. 12372; OR

☒ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

**17. By signing this application, I certify (1) to the statements contained in the list of certifications\* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances \* and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)**

☒ I agree\*

\* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

**18. SFLL or OTHER EXPLANATORY DOCUMENTATION**

File Name:

**19. AUTHORIZED REPRESENTATIVE**

Prefix: Ms. First Name\*: Andria Middle Name: Last Name\*: Adler Suffix:

Position/Title\*: Grant Administrator

Organization Name\*: The Research Foundation for the State University of New York

Department: OSP

Division: OVRP

Street1\*: W5510 Melville Library

Street2: Stony Brook University

City\*: Stony Brook

County: Suffolk

State\*: NY: New York

Province:

Country\*: USA: UNITED STATES

ZIP / Postal Code\*: 117943362

Phone Number\*: 631-632-1610 Fax Number: 631-632-6963 Email\*: andria.adler@stonybrook.edu

**Signature of Authorized Representative\***

Andria Adler

**Date Signed\***

03/19/2015

**20. PRE-APPLICATION** File Name:**21. COVER LETTER ATTACHMENT** File Name: P20\_cover\_LETTER03.18.15.pdf

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**Component  
Summary**

<b>Components</b>	<b>Component Project Title</b>	<b>Organization Name</b>	<b>Contact PD/PI Name or Project Lead Name</b>
Overall	1/2: Partnership to study racial/ethnic differences in GI cancer biology	The Research Foundation for SUNY, Stony Brook University	Li, Ellen
Admin-Core-001 (253)	Administrative Core	The Research Foundation for SUNY, Stony Brook University	Li, Ellen
Project-001 (836)	Pilot Project Research Project 1	The Research Foundation for SUNY, Stony Brook University	Li, Ellen
Project-002 (206)	Pilot Project Research Project 2	The Research Foundation for SUNY, Stony Brook University	Li, Ellen
Train-Edu-Prog-001 (551)	Training and Education Program	The Research Foundation for SUNY, Stony Brook University	Stewart, Mark

**Project/Performance  
Site Location(s) Summary**

<b>Applicant Organization</b>	<b>City</b>	<b>State/Province</b>	<b>Country</b>
The Research Foundation for SUNY, Stony Brook University	STONY BROOK	NY	UNITED STATES

<b>Organization Name</b>	<b>City</b>	<b>State/Province</b>	<b>Country</b>	<b>Component</b>
Cold Spring Harbor Laboratory	Cold Spring Harbor	NY	UNITED STATES	Overall
The Research Foundation for SUNY - Downstate Medical Center	Brooklyn	NY	UNITED STATES	Admin-Core-001 (253)
The Research Foundation for SUNY - Downstate Medical Center	Brooklyn	NY	UNITED STATES	Train-Edu-Prog-001 (551)
The Research Foundation for SUNY Downstate Medical Center	Brooklyn	NY	UNITED STATES	Overall
The Research Foundation for SUNY, Downstate Medical Center	Brooklyn	NY	UNITED STATES	Project-001 (836)
The Research Foundation for SUNY, Downstate Medical Center	Brooklyn	NY	UNITED STATES	Project-002 (206)
The Research Foundation for SUNY, Stony Brook University	STONY BROOK	NY	UNITED STATES	Admin-Core-001 (253)
The Research Foundation for SUNY, Stony Brook University	STONY BROOK	NY	UNITED STATES	Overall
The Research Foundation for SUNY, Stony Brook University	STONY BROOK	NY	UNITED STATES	Project-001 (836)
The Research Foundation for SUNY, Stony Brook University	STONY BROOK	NY	UNITED STATES	Project-002 (206)
The Research Foundation for SUNY, Stony Brook University	STONY BROOK	NY	UNITED STATES	Train-Edu-Prog-001 (551)

Human Subjects  
Clinical Trial  
Human Embryonic Stem Cells  
Vertebrate Animals  
Summary

Components	Human Subjects	Clinical Trial	HESC Involved	Vertebrate Animals
Overall	Y	N	N	Y
Admin-Core-001 (253)	N	N	N	N
Project-001 (836)	Y	N	N	N
Project-002 (206)	Y	N	N	Y
Train-Edu-Prog-001 (551)	N	N	N	N

## Composite Application Budget Summary

Categories	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Salary, Wages and Fringe Benefits	105,237	105,237	105,237	105,237	0	420,948
Equipment	0	0	0	0	0	0
Travel	1,322	1,174	1,102	1,078	0	4,676
Participant/Trainee Support Costs	0	0	0	0	0	0
Other Direct Costs (excluding Consortium)	6,500	6,500	6,500	6,500	0	26,000
Consortium Costs	80,941	81,089	81,161	81,185	0	324,376
Direct Costs	194,000	194,000	194,000	194,000	0	776,000
Indirect Costs	109,174	116,808	116,811	116,811	0	459,604
Total Direct and Indirect Costs	303,174	310,808	310,811	310,811	0	1,235,604

## Total Direct Costs less Consortium F&amp;A

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

Category	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Total Direct Costs less Consortium F&A	150,372	144,131	144,086	144,072	0	582,661

## Component Budget Summary

Components	Categories	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Admin-Core-001 (253)	Salary, Wages and Fringe Benefits	79,090	79,090	79,090	79,090	0	316,360
	Equipment	0	0	0	0	0	0
	Travel	1,322	1,174	1,102	1,078	0	4,676
	Participant/Trainee Support Costs	0	0	0	0	0	0
	Other Direct Costs (excluding Consortium)	0	0	0	0	0	0
	Consortium Costs	4,116	4,155	4,187	4,187	0	16,645
	Direct Costs	84,528	84,419	84,379	84,355	0	337,681
	Indirect Costs	49,141	49,108	49,086	49,072	0	196,407
<b>TOTALS</b>	Total Direct and Indirect Costs	133,669	133,527	133,465	133,427	0	<b>534,088</b>
Project-001 (836)	Salary, Wages and Fringe Benefits	10,658	10,658	10,658	10,658	0	42,632
	Equipment	0	0	0	0	0	0
	Travel	0	0	0	0	0	0
	Participant/Trainee Support Costs	0	0	0	0	0	0
	Other Direct Costs (excluding Consortium)	3,000	3,000	3,000	3,000	0	12,000
	Consortium Costs	20,688	13,717	13,737	13,737	0	61,879
	Direct Costs	34,346	27,375	27,395	27,395	0	116,511
	Indirect Costs	14,495	17,808	17,820	17,820	0	67,943
<b>TOTALS</b>	Total Direct and Indirect Costs	48,841	45,183	45,215	45,215	0	<b>184,454</b>

Project-002 (206)	Salary, Wages and Fringe Benefits	8,298	8,298	8,298	8,298	0	33,192
	Equipment	0	0	0	0	0	0
	Travel	0	0	0	0	0	0
	Participant/Trainee Support Costs	0	0	0	0	0	0
	Other Direct Costs (excluding Consortium)	3,000	3,000	3,000	3,000	0	12,000
	Consortium Costs	44,137	51,217	51,237	51,261	0	197,852
	Direct Costs	55,435	62,515	62,535	62,559	0	243,044
	Indirect Costs	33,697	38,051	38,064	38,078	0	147,890
<b>TOTALS</b>	Total Direct and Indirect Costs	89,132	100,566	100,599	100,637	0	<b>390,934</b>
Train-Edu-Prog-001 (551)	Salary, Wages and Fringe Benefits	7,191	7,191	7,191	7,191	0	28,764
	Equipment	0	0	0	0	0	0
	Travel	0	0	0	0	0	0
	Participant/Trainee Support Costs	0	0	0	0	0	0
	Other Direct Costs (excluding Consortium)	500	500	500	500	0	2,000
	Consortium Costs	12,000	12,000	12,000	12,000	0	48,000
	Direct Costs	19,691	19,691	19,691	19,691	0	78,764
	Indirect Costs	11,841	11,841	11,841	11,841	0	47,364
<b>TOTALS</b>	Total Direct and Indirect Costs	31,532	31,532	31,532	31,532	0	<b>126,128</b>
<b>TOTALS</b>		<b>303,174</b>	<b>310,808</b>	<b>310,811</b>	<b>310,811</b>	<b>0</b>	<b>1,235,604</b>

## Categories Budget Summary

Categories	Components	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
R&R Budget - Senior/Key Person Funds Requested	Admin-Core-001 (253)	79,090	79,090	79,090	79,090	0	316,360
	Project-001 (836)	10,658	10,658	10,658	10,658	0	42,632
	Project-002 (206)	8,298	8,298	8,298	8,298	0	33,192
	Train-Edu-Prog-001 (551)	7,191	7,191	7,191	7,191	0	28,764
<b>TOTALS</b>		105,237	105,237	105,237	105,237	0	<b>420,948</b>
R&R Budget - Other Personnel Funds Requested	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	<b>0</b>
R&R Budget - Section A & B. Total Salary, Wages and Fringe Benefits (A+B)	Admin-Core-001 (253)	79,090	79,090	79,090	79,090	0	316,360
	Project-001 (836)	10,658	10,658	10,658	10,658	0	42,632
	Project-002 (206)	8,298	8,298	8,298	8,298	0	33,192
	Train-Edu-Prog-001 (551)	7,191	7,191	7,191	7,191	0	28,764
<b>TOTALS</b>		105,237	105,237	105,237	105,237	0	<b>420,948</b>

R&R Budget - Section C. Total Equipment	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Domestic Travel	Admin-Core-001 (253)	1,322	1,174	1,102	1,078	0	4,676
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		1,322	1,174	1,102	1,078	0	4,676
R&R Budget - Foreign Travel	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Section D. Total Travel	Admin-Core-001 (253)	1,322	1,174	1,102	1,078	0	4,676
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0

<b>TOTALS</b>		1,322	1,174	1,102	1,078	0	<b>4,676</b>
R&R Budget - Tuition/Fees/Health Insurance	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	<b>0</b>
R&R Budget - Stipends	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	<b>0</b>
R&R Budget - Trainee Travel	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	<b>0</b>
R&R Budget - Subsistence	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0

	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Other Participants/Trainee Support Costs	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Section E. Total Participants/Trainee Support Costs	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Materials and Supplies	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	2,500	2,500	2,500	2,500	0	10,000
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	500	500	500	500	0	2,000
<b>TOTALS</b>		3,000	3,000	3,000	3,000	0	12,000
R&R Budget - Publication Costs	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	500	500	500	500	0	2,000

	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		500	500	500	500	0	2,000
R&R Budget - Consultant Services	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - ADP/Computer Services	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Subawards/Consortium/Contractual Costs	Admin-Core-001 (253)	4,116	4,155	4,187	4,187	0	16,645
	Project-001 (836)	20,688	13,717	13,737	13,737	0	61,879
	Project-002 (206)	44,137	51,217	51,237	51,261	0	197,852
	Train-Edu-Prog-001 (551)	12,000	12,000	12,000	12,000	0	48,000
<b>TOTALS</b>		80,941	81,089	81,161	81,185	0	324,376

R&R Budget - Equipment or Facility Rental User Fees	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Alterations and Renovations	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Other Direct Cost 1	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	3,000	3,000	3,000	3,000	0	12,000
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		3,000	3,000	3,000	3,000	0	12,000
R&R Budget - Other Direct Cost 2	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0

<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Other Direct Cost 3	Admin-Core-001 (253)	0	0	0	0	0	0
	Project-001 (836)	0	0	0	0	0	0
	Project-002 (206)	0	0	0	0	0	0
	Train-Edu-Prog-001 (551)	0	0	0	0	0	0
<b>TOTALS</b>		0	0	0	0	0	0
R&R Budget - Section F. Total Other Direct Cost	Admin-Core-001 (253)	4,116	4,155	4,187	4,187	0	16,645
	Project-001 (836)	23,688	16,717	16,737	16,737	0	73,879
	Project-002 (206)	47,137	54,217	54,237	54,261	0	209,852
	Train-Edu-Prog-001 (551)	12,500	12,500	12,500	12,500	0	50,000
<b>TOTALS</b>		87,441	87,589	87,661	87,685	0	350,376
R&R Budget - Section G. Total Direct Cost (A thru F)	Admin-Core-001 (253)	84,528	84,419	84,379	84,355	0	337,681
	Project-001 (836)	34,346	27,375	27,395	27,395	0	116,511
	Project-002 (206)	55,435	62,515	62,535	62,559	0	243,044
	Train-Edu-Prog-001 (551)	19,691	19,691	19,691	19,691	0	78,764
<b>TOTALS</b>		194,000	194,000	194,000	194,000	0	776,000
R&R Budget - Section H. Indirect Costs	Admin-Core-001 (253)	49,141	49,108	49,086	49,072	0	196,407
	Project-001 (836)	14,495	17,808	17,820	17,820	0	67,943
	Project-002 (206)	33,697	38,051	38,064	38,078	0	147,890

	Train-Edu-Prog-001 (551)	11,841	11,841	11,841	11,841	0	47,364
<b>TOTALS</b>		109,174	116,808	116,811	116,811	0	<b>459,604</b>
R&R Budget - Section I. Total Direct and Indirect Costs (G +H)	Admin-Core-001 (253)	133,669	133,527	133,465	133,427	0	534,088
	Project-001 (836)	48,841	45,183	45,215	45,215	0	184,454
	Project-002 (206)	89,132	100,566	100,599	100,637	0	390,934
	Train-Edu-Prog-001 (551)	31,532	31,532	31,532	31,532	0	126,128
<b>TOTALS</b>		303,174	310,808	310,811	310,811	0	<b>1,235,604</b>

**Senior/Key Personnel  
Summary**

Name	Organization	Role on Project	Components
Li, Ellen	The Research Foundation for SUNY, Stony Brook University	PD/PI(Contact)	Overall
Bucobo, Juan Carlos	The Research Foundation for SUNY, Stony Brook University	Co-Investigator	Project-002 (206)
Denoya, Paula I	The Research Foundation for SUNY, Stony Brook University	Co-Investigator	Project-001 (836)
Li, Ellen	The Research Foundation for SUNY, Stony Brook University	Other: Core Lead	Admin-Core-001 (253)
Li, Ellen	The Research Foundation for SUNY, Stony Brook University	Other: Project Lead	Project-001 (836)
Li, Ellen	The Research Foundation for SUNY, Stony Brook University	Other: Project Lead	Project-002 (206)
Li, Ellen	The Research Foundation for SUNY, Stony Brook University	Co-Investigator	Train-Edu-Prog-001 (551)
Mackenzie, Gerardo Guillermo	Stony Brook University	Co-Investigator	Project-002 (206)
Martello-Rooney, Laura	The Research Foundation for SUNY, Downstate Medical Center	Other: Subsite Co-Investigator	Project-001 (836)
Martello-Rooney, Laura	The Research Foundation for SUNY, Downstate Medical Center	Other: Subsite Co-Investigator	Project-002 (206)
Salifu, Moro	The Research Foundation for SUNY, Downstate Medical Center	Co-Investigator	Admin-Core-001 (253)
Salifu, Moro	The Research Foundation for SUNY, Downstate Medical Center	Other: Subsite Lead	Project-001 (836)
Salifu, Moro	The Research Foundation for SUNY, Downstate Medical Center	Other: Subsite Lead	Project-002 (206)
Saltz, Joel H.	Stony Brook University	Co-Investigator	Admin-Core-001 (253)
Senathirajah, Yalini	SUNY Downstate	Co-Investigator	Admin-Core-001 (253)
Stewart, Mark	The Research Foundation for SUNY, Downstate Medical Center	Other: Subsite Co-Investigator	Project-001 (836)
Stewart, Mark	The Research Foundation for SUNY, Downstate Medical Center	Other: Subsite Co-Investigator	Project-002 (206)
Stewart, Mark	The Research Foundation for SUNY, Downstate Medical Center	Other: Project Lead	Train-Edu-Prog-001 (551)
Thompson, Patricia Ann	Stony Brook university	Co-Investigator	Train-Edu-Prog-001 (551)
Vignesh, Shivakumar	SUNY Downstate	Co-Investigator	Project-002 (206)

Williams, Jennie	The Research Foundation for SUNY, Stony Brook University	Co-Investigator	Project-001 (836)
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Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Juan Carlos Bucobo, M.D.		POSITION TITLE Assistant Professor of Medicine	
eRA COMMONS USER NAME (credential, e.g., agency login) JCBucobo			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
State University of New York at Buffalo, NY	B.S.	06/96	Biochemical Pharm.
Sackler School of Medicine, New York State/American Program, Tel Aviv University, Tel Aviv, Israel	MD	06/03	Medicine
Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY		06/04	Medical Internship
State University of New York at Stony Brook, Stony Brook, NY		06/06	Medical Residency
State University of New York at Stony Brook, Stony Brook, NY		06/09	Gastroenterology Fellowship
Cedars-Sinai Medical Center, Los Angeles, California		06/10	Advanced Fellowship, Interventional Endoscopy

**A. Personal Statement:**

As a gastroenterologist specializing in interventional endoscopy, I have a strong commitment to the diagnosis, treatment and research of pancreatic cancer. As part of my clinical practice, I frequently diagnose patients with pancreatic cancer by endoscopic ultrasound and appreciate the impact of the disease on the lives of those afflicted. This translational research project offers the opportunity to better understand the biology of this aggressive and lethal disease. I currently serve as the Director of Endoscopy at Stony Brook University Hospital and have been responsible for maintaining our endoscopy database both for quality assurance and clinical research. I appreciate the impact of interventions directed at providers and underserved patient populations in increasing awareness of colorectal cancer and pancreatic cancer. I have served as a principal investigator and co-investigator on several retrospective and prospective trials of various endoscopic techniques and interventions directed at reducing racial disparities. My experience with these projects as well as my service with a major gastrointestinal endoscopy society and journal has allowed me to understand the rigor of conducting a well-executed research study. I have been an active member of the Stony Brook Cancer Center GI Interest group and the Long Island Pancreatic Research Group. As a member of the interventional endoscopy section of the Division of Gastroenterology, I will obtain and assist in the standardization of obtaining EUS-guided pancreatic cancer biopsies for the development of organoids.

**Positions and Honors:****Positions and Employment**

Program Director/Principal Investigator (Last, First, Middle):

*Assistant Professor of Medicine*

Stony Brook Medicine

State University of New York at Stony Brook—Stony Brook, NY

2010-Present

*Director of Endoscopy*

Stony Brook University Hospital

State University of New York at Stony Brook—Stony Brook, NY

2012-Present

**Other Experience and Professional Memberships**

Editor, Gastrointestinal Endoscopy (GIE), Fellows' Corner section

2008-2010

Editorial Review Board, Gastrointestinal Endoscopy (GIE)

2011-2013

Diversity Committee, ASGE

2014-Present

**B. Peer-reviewed Publications:**

1. Buscaglia JM, Kapoor S, Clarke JO, **Bucobo JC**, Giday SA, Magno P, Yong E, Mullin GE. Enhanced Diagnostic Yield with Prolonged Small Bowel Transit Time during Capsule Endoscopy. *Int J Med Sci* 2008; 5:303-308
2. **Bucobo JC**, Buscaglia JM. The on-call fellow—answering the after-hours call. *Gastrointestinal Endoscopy* 2009; 69(2):304-6.
3. **Bucobo JC**. Choosing a subspecialty in gastroenterology: using your resources. *Gastrointestinal Endoscopy* 2009;70(4):749-50.
4. Harris MD, **Bucobo JC**, Buscaglia JM. Pancreatitis, panniculitis, polyarthrititis syndrome successfully treated with EUS-guided cyst-gastrostomy. *Gastrointest Endosc*. 2010 Aug;72(2):456-8.
5. Jayaraman V, Wilkinson MN, Nagula S, Siebel M, **Bucobo JC**, Zee S, Buscaglia JM. Primary jejunal angiosarcoma: an extremely rare tumor diagnosed by means of anterograde spiral enteroscopy. *Endoscopy*. 2011;43 Suppl 2 UCTN:E219-20. Epub 2011 May 16.
6. Nagula S, Gaidos J, Draganov PV, **Bucobo JC**, Cho B, Hernandez Y, Buscaglia JM. Retrograde spiral enteroscopy: feasibility, success, and safety in a series of 22 patients. *Gastrointest Endosc*. 2011 Sep;74(3):699-702.
7. Buscaglia J, Nagula S, Yuan J, **Bucobo JC**, Kumar A, Forsmark CE, Draganov PV. The practice of evidence-based medicine (EBM) in gastroenterology: discrepancies between EBM familiarity and EBM competency. *Therap Adv Gastroenterol*. 2011 Sep;4(5):283-94.
8. Buscaglia JM, Karas J, Palladino N, Fakhoury J, Denoya PI, Nagula S, **Bucobo JC**, Bishawi M, Bergamaschi R. Simulated transanal NOTES sigmoidectomy training improves the responsiveness of surgical endoscopists. *Gastrointest Endosc*. 2014 Feb 8. pii: S0016-5107
9. Son, P., Lane, D. S., Messina, C. R., Yang, J., Zhu, J., Li, E., Nagula S., Lascarides CE., **Bucobo, J. C.** (2014). Impact of Project SCOPE on Racial/Ethnic Disparities in Screening Colonoscopies. *Journal of Racial and Ethnic Health Disparities*, 1-10.
10. Nagula S, Pourmand K, Aslanian HR, **Bucobo JC**, et al. EUS-fine needle aspiration (FNA) vs. EUS-fine needle biopsy (FNB) for solid mass lesions: interim analysis of a large multicenter, randomized clinical trial. *Gastrointest Endosc* 2013;77 5 Suppl:AB357–AB358.

**C. Research Support**ACTIVE NoneCOMPLETED

Bucobo (PI)

01/01/13 -12/31/13

Medicine Seed Grant

Reducing racial/ethnic disparities in early colon cancer diagnosis

Examined the impact of Project SCOPE on screening colonoscopies in racial ethnic minorities.

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Paula I. Denoya, M.D.		POSITION TITLE Assistant Professor of Surgery	
eRA COMMONS USER NAME (credential, e.g., agency login) PDENOYA			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
New York University, NYC, NY	BA	06/98	Biology
Mount Sinai School of Medicine, NYC, NY	MD	06/02	Medicine
Mount Sinai School of Medicine, NYC, NY	Residency	06/07	Surgery
Cleveland Clinic Florida, Weston, FL	Research Fellow	06/08	Colorectal Surgery
Cleveland Clinic Florida, Weston, FL	Clinical Fellow	06/09	Colorectal Surgery

**A. Personal Statement:**

As an academic colorectal surgeon, I have made a strong commitment to conducting clinical translational research in colorectal cancer. I was the PI of an institutional seed award in launching a collaborative project between Stony Brook University and Cold Spring Harbor Laboratories (Drs. Antoniou and McCombie) in linking high resolution methylation mapping to mRNA (RNA-Seq expression profiling). I am the senior author of a manuscript reporting our initial expression profiling experiments using a cultured colon cancer cell line. I am delighted at continuing this project now with a focus on examining racial and ethnic differences in colorectal cancer biology in collaboration with the other members of this investigative team. I and other members of the colorectal division have worked closely with Dr. Li to expedite the prospective banking of all colorectal surgical resections performed in my division and to assist in the longitudinal tracking of the patients we have recruited to donate their tissues and clinical information. I have been an active participant of the Stony Brook Cancer Center GI interest group since its inception in July 2012. In addition I have a personal interest in reducing racial and ethnic disparities in colorectal cancer outcome and in training underrepresented minority students in cancer research. I look forward to serving as a clinical co-mentor for the proposed Scholars in BioMedical Sciences in Cancer Health Disparities and in participating in the educational workshops, sponsored by the Training and Education Program.

**B. Positions and Honors:**Positions

2009-present      Assistant Professor of Surgery, Division of Colon Rectal Surgery

Honors

1994-1998      NYU Presidential Scholarship  
 1994-1998      Pfizer Inc. Corporate National Merit Scholarship  
 1994-1998      Academic Achievement Program  
 2002      Eugene W. Friedman MD Award for Clinical Excellence  
 2006      Humanism and Excellence in Teaching Award. Mount Sinai School of Medicine, NY, NY  
 2008      Third prize for clinical research: P. Denoya, S. Shawki, D. Sands, J. Nogueras, E. Weiss, S. Wexner. "Colorectal anastomotic stricture: Is it caused by inadequate colonic mobilization?" 19th Annual Fellow, Resident and Medical Student Surgical Research Forum of the South Florida Chapter of the American College of Surgeons. April 17, 2008. Weston FL  
 2012      First prize for podium presentation: Stein SA, Fakhoury M, Denoya P, Bishawi M, Bergamaschi R. Surgical site infection rates following conventional vs. hand-assisted colorectal resections. New York Society of Colon and Rectal Surgeons (NYSCRS), New York, NY

Program Director/Principal Investigator (Last, First, Middle):

- 2012 First prize for poster presentation: Zakhaleva J, Tam J, Karas JR, Fakhoury M, Fakhoury J, Gregg TR, Bishawi M, Denoya P, Bergamaschi R. Intraoperative esophageal Dopplerguided intravenous fluid administration: a randomized controlled trial. New York Society of Colon and Rectal Surgeons (NYSCRS), New York, NY

### C. Peer-reviewed Publications:

1. **Denoya PI**, Schluender SJ, Bub DS, Gorfine SR, Bauer JJ. Delayed Kock pouch nipple valve failure: is revision indicated? *Dis Colon Rectum*. 2008;51:1544-7.
2. **Denoya PI**, Fakhoury M, Chang K, Fakhoury J, Bergamaschi R. Dearterialization with mucopexy versus haemorrhoidectomy for grade III or IV haemorrhoids: short-term results of a double-blind randomized controlled trial. *Colorectal Dis*. 2013;15:1281-8.
3. Zakhaleva J, Tam J, **Denoya PI**, Bishawi M, Bergamaschi R. The impact of intravenous fluid administration on complication rates in bowel surgery within an enhanced recovery protocol: a randomized controlled trial. *Colorectal Dis*. 2013;15:892-9.
4. Xu X, Zhang Y, Williams J, Antoniou E, McCombie WR, Wu S, Zhu W, Davidson NO, **Denoya P**, Li E. Parallel comparison of Illumina RNA-Seq and Affymetrix microarray platforms on transcriptomic profiles generated from 5-aza-deoxy-cytidine treated HT-29 colon cancer cells and simulated datasets. *BMC Bioinformatics* 2013, 14(Suppl 9):S1 PMC3687991
5. Bishawi M, Fakhoury M, **Denoya PI**, Stein S, Bergamaschi R. Surgical site infection rates: open versus hand-assisted colorectal resections. *Tech Coloproctol*. 2014;18:381-6.
6. Buscaglia JM, Karas J, Palladino N, Fakhoury J, **Denoya PI**, Nagula S, Bucobo JC, Bishawi M, Bergamaschi R. Simulated transanal NOTES sigmoidectomy training improves the responsiveness of surgical endoscopists. *Gastrointest Endosc*. 2014; 80:126-32.
7. Foppa C, **Denoya PI**, Tarta C, Bergamaschi R. Indocyanine green fluorescent dye during bowel surgery: Are the blood supply "guessing days" over? *Tech Coloproctol*. 2014; 18:753-8.
8. Buscaglia JM, Fakhoury J, Loyal J, **Denoya PI**, Kazi E, Stein SA, Scriven R, Bergamaschi R. Simulated colonoscopy training using a low-cost physical model improves responsiveness of surgery interns. *Colorectal Dis*. 2014 Dec 24. doi: 10.1111/codi.12883. [Epub ahead of print]

### D Research Support

ACTIVE None

#### COMPLETED

Stony Brook University Internal Targeted Research Opportunity Program FUSION Seed Award 37298 (PI Denoya)

High Definition Profiling of Human Colorectal Cancer Methylation Seed award to pilot generation of RNA-Seq and reduced representation bisulfite sequencing data in colorectal cancer biospecimens.

Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Li, Ellen M.D.-Ph.D.		POSITION TITLE Professor of Medicine	
eRA COMMONS USER NAME (credential, e.g., agency login) ELLENLI1			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Stanford University, Stanford, CA	B.S.	1974	Chemistry
Washington University-St. Louis, St. Louis, MO	M.D.	1980	Medicine
Washington University-St. Louis, St. Louis, MO	Ph.D.	1980	Biochemistry
Massachusetts General Hospital, Boston, MA	Residency	1980-1983	Internal Medicine
Barnes Hospital, St. Louis MO	Fellow	1983-1984	Gastroenterology
Washington University-St. Louis, St. Louis, MO	Post-doc	1984-1986	Molecular Biology

**A. Personal Statement**

Over the past 10 years the focus of my research efforts has been to build patient data/tissue repositories that will facilitate clinical translational research in digestive diseases. I was the founding Director of the Washington University Digestive Diseases Research Core Center (2000) and the driving force in building its Center's Biobank (2005). On moving to Stony Brook University in 10/2009 for family reasons, I began building a patient data/tissue repository there, using the same standard operating procedures that I implemented at Washington University-St. Louis and to forge interdepartmental (adult GI, pediatric GI, Surgery Pathology) collaborative projects to drive the collection effort. Because basic scientists and clinicians at Stony Brook University were very interested in applying next generation sequencing methodology towards characterizing racial/ethnic differences in GI cancer biology I was instrumental in forging collaborations between these investigators and investigators at Cold Spring Harbor Laboratories, as evidenced by the recent publication of jointly authored manuscripts, and I was instrumental in developing collaborative interactions with clinicians and basic scientists at SUNY Downstate Medical Center. Furthermore, I have supported bioinformatics and biostatistical analysis to of the data generated by investigators, such as Dr. Williams, by funding Applied Mathematics and Statistics graduate students/postdoctoral fellows who are jointly trained by Department of BioMedical Informatics faculty and myself. As a senior faculty member at SUNY Stony Brook I have a deep commitment to assist with investigators, such as Dr. Williams, with the analysis of the data towards increasing diversity in translational research and have been engaged mentored URM and non-URM trainees (high school on) and mentoring URM and non-URM faculty at multiple institutions. As Chief of the Division of Gastroenterology and Hepatology and more recently the Director of Colorectal Cancer Screening in the Stony Brook Cancer Center in am empowered to better align clinical practice with our clinical translational research efforts.

1973	Phi Beta Kappa, Stanford University
1974-1978	Mr. and Mrs. Spencer T. Olin Fellowship for Women in Science
1980	Alpha Omega Alpha
1980-83	Intern and Resident, Medicine, Massachusetts General Hospital, Boston, MA
1983-1986	Fellow in Medicine (Gastroenterology), Washington University School of Medicine
1985-1991	Lucille P. Markey Scholar, 1985
1986-1992	Assistant Professor of Medicine, Washington University, St. Louis, MO
1987-1992	Assistant Professor of Biochemistry and Molecular Biophysics, Washington University
1992-1995	NIH Research Career Development Award DK02072
1992-1997	Associate Professor of Medicine, Washington University, St. Louis, MO
1992-present	Associate Professor of Biochemistry and Molecular Biophysics, Washington University

## Principal Investigator (Last, First, Middle):

1993 GRG-AGA Young Investigator Award  
 1995-2000 Burroughs Wellcome Fund Toxicology Scholar Award  
 1996-1997 Co-director, Division of Gastroenterology, Washington University  
 1997-present Professor of Medicine, Washington University  
 2000-2009 Director of the Washington University Digestive Diseases Research Core Center  
 2009-present Professor of Medicine and Molecular Genetics and Microbiology, Stony Brook University  
 2012 Stony Brook University Education Opportunities Program/ Advancement on Individual Merit Distinguished Advocate Award  
 2012-2013 Interim Chief, Division of Gastroenterology and Hepatology, Stony Brook University  
 2013-2014 SUNY Presidential Fellow, SUNY Health Network of Excellence  
 2013-present Chief, Division of Gastroenterology and Hepatology, Stony Brook University

Professional Societies

Member, American Gastroenterological Association, Research Committee  
 Member, American Society for Clinical Investigators  
 Member, Association of American Physicians

**C. Selected Peer-reviewed Publications (out of 87)**

1. Cadwell K, Liu J, Brown SL, Miyoshi H, Loh J, Lennerz J, Kishi C, Carrero JA, Hunt S, Stone C, Brunt EM, Sleckman B, Li E, Mizushima N, Stappenbeck TS, Virgin HW 4th. A key role for autophagy and the autophagy gene Atg16L1 in murine and human intestinal Paneth cells. *Nature*. 2008; 456: 259-63. PMC: 2695978.
2. Hamm CM, Reimers MA, McCullough CK, Gorbe EB, Lu J, Gu CC, Li E, Dieckgraefe BK, Gong Q, Stappenbeck TS, Stone CD, Dietz DW, Hunt SR. NOD2 status and human ileal gene expression. *Inflamm Bowel Dis*. 2010;16:1649-57.
3. Frank DN, Robertson CE, Hamm CM, Kpadeh Z, Zhang T, Chen H, Zhu W, Sartor RB, Boedeker EC, Harpaz N, Pace NR, Li E. Disease phenotype and genotype are associated with shifts in intestinal-associated microbiota in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2011; 17:179-84 PMC3834564
4. Chen H, Lee A, Bowcock A, Zhu W, Li E, Ciorba M, Hunt S. Influence of Crohn's disease alleles and smoking on disease location. *Dis Colon Rectum*. 2011; 54:1020-5. PMC3403696
5. Frank DN, Zhu W, Sartor RB Li E. Investigating the biological and clinical significance of human dysbiosis. *Trends Microbiol*. 2011; 19:427-34 PMC3164499
6. Zhang T, Song B, Zhu W, Xu X, Gong Q, Morando C, Dassopoulos T, Newberry RD, Hunt S R, Li E. An ileal Crohn's disease gene signature based on whole human genome expression profiles of disease unaffected ileal mucosal biopsies. *PLoS One*, 2012, 7:e37139 PMC3351422
7. Li E, Hamm CM, Gulati AS, Sartor RB, Chen H, Wu X, Zhang T, Rohlf FJ, Zhu W, Gu C, Robertson CE, Pace NR, Boedeker EC, Harpaz N, Yuan J, Weinstock GM, Sodergren E, Frank DN. Inflammatory bowel diseases phenotype, *C. difficile* and NOD2 genotype are associated with shifts in human ileum associated microbial composition. *PLoS One*, 2012; 7:e26284 PMC3374607
8. Zhang T, DeSimone RA, Jiao X, Rohlf FJ, Zhu W, Gong Q, Hunt SR, Dassopoulos T, Newberry RD, Sodergren E, Weinstock G, Robertson CE, Frank DN, Li E. Host genes related to Paneth cells and xenobiotic metabolism are associated with shifts in human ileum-associated microbial composition. *PLoS One*, 2012; 7:e30044 PMC3374611
9. Katz M, Parrish ME, Li E, Zhang Y, Zhu W, Shroyer K, Bergamaschi R, Williams J. The effect of race/ethnicity on the age of colon cancer diagnosis. *J Health Disparities Research and Practice* 2013; 6:62-69
10. Wu X, Berkow K, Frank DN, Li E, Gulati AS, Zhu W. Comparative analysis of microbiome measurement platforms using latent variable structural equation modeling. *BMC Bioinformatics*. 2013;14:79 PMC3608994
11. Xu X, Zhang Y, Williams J, Antoniou E, McCombie WR, Wu S, Zhu W, Davidson NO, Denoya P, Li E. Parallel comparison of Illumina RNA-Seq and Affymetrix microarray platforms on transcriptomic

Principal Investigator (Last, First, Middle):

- profiles generated from 5-aza-deoxy-cytidine treated HT-29 colon cancer cells and simulated datasets. BMC Bioinformatics 2013, 14(Suppl 9):S1 PMC3687991
12. Tong M, Li X, Wegener Parfrey L, Roth B, Ippoliti A, Wei B, Borneman J, McGovern DP, Frank DN, Li E, Horvath S, Knight R, Braun J. A modular organization of the human intestinal mucosal microbiota and its association with inflammatory bowel disease. PLoS One. 2013;:e80702. PMC3834335
  13. Li E, Ji P, Ouyang N, Zhang Y, Wang XY, Rubin DC, Davidson NO, Bergamschi R, Shroyer KR, Birke S, Zhu W, Williams JI. Differential expression of miRNAs in colon cancer between African and Caucasian Americans: implications for cancer racial health disparities. Int J. Oncol, 2014; 45:587-594
  14. Son P, Lane DS, Messina CR, Yang J, Zhu J, Li E, Nagula S, Lascarides CE, Bucobo JC. Impact of Project SCOPE on racial/ethnic disparities in colorectal cancer screening. J. Racial and Ethnic Health Disparities. 2014; 1: 110-119.
  15. Lee A, Kanuri N, Zhang Y, Sayuk GS, Li E, Ciorba MA. Lee A, Kanuri N, Zhang Y, Sayuk GS, Li E, Ciorba MA. IDO1 and IDO2 non-synonymous gene variants: correlation with Crohn's disease risk and clinical phenotype. PLoS One. 2014;9: e115848. PMC4277413
  16. Wang X, Yu X, Zhu W, McCombie WR, Antoniou E, Powers RS, Davidson NO, Li E, Williams J. A trimming-and-retrieving alignment scheme for reduced representation bisulfite sequencing. Bioinformatics. 2015 Feb 13. [Epub ahead of print]

## D. Research Support

### ACTIVE

SFARI Grant Number: 239729 (Li) 10/1/2012-03/31/2015

Autism, GI symptoms and the enteric microbiota

This study aims to characterize the fecal microbiota and GI symptoms in the autism proband and the unaffected sibling of ~300 families registered within the Simons Simplex Collection (SSC) that have consented for recontact.

Role: PI

Overlap: No overlap

### COMPLETED

Crohn's Colitis Foundation of America (Sartor) 1/01/11-12/31/13

Influence of Crohn's- related genetic defects in innate immune function on intestinal microbial composition and function.

Focused on correlating results of genetic animal studies and pediatric patient based samples, on the effect of Crohn's related genetic defects in innate immune function.

Role: Co-PI

Sinai-Helmsley Alliance for Research Excellence (Sartor) 2012-12/31/13

Postoperative recurrence of Crohn's disease

Role: co-investigator

To analyze ileal microbiota from ileal CD patients undergoing ileo-colic resection recruited through SHARE participants to test the hypothesis that decreased Faecalibacterium spp are associated with an increased risk of endoscopic recurrence.

Role: co-investigator

Simons Foundation (Li) 9/2009-8/2012

Establishing a Digestive Diseases Research Tissue Procurement Facility

Building an infrastructure for prospective collection of clinical data linked to blood and tissue samples in patients with digestive diseases.

Role: PI

1UH2DK083994-01 (Li) 06/01/09-05/31/12

NIH/NIDDK

Effect of Crohn's Disease Risk Alleles on Enteric Microbiota

Principal Investigator (Last, First, Middle):

Determine the effect of Crohn's disease risk alleles on ileal mucosal associated bacteria in patients with ileal Crohn's disease, patients with inflammatory bowel diseases not affecting the ileum and patients without inflammatory bowel diseases.

Role: PI

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Gerardo G. MACKENZIE</b>	POSITION TITLE <b>Assistant Professor</b>		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>GMACKENZIE</b>			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of Buenos Aires, Argentina	B.S./M.S.	12/99	Biochemistry
University of Buenos Aires, Argentina	Ph.D.	05/04	Cell Biology
University of California, Davis, CA	Postdoc	09/07	Cell Biology
Stony Brook University, Stony Brook, NY	Senior Postdoc	10/09	Cancer Research

**Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.**

**A. Personal Statement:**

The goal of the proposed research is to perform feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research. In this proposal, I will lead the Stony Brook effort of the pilot project # 2, which will test the hypothesis that genetic and gene expression alterations in pancreatic cancer underlie the increased incidence, mortality, and treatment resistance observed in under represented minorities (URMs). Working closely with Dr. David Tuveson and his laboratory at CSHL, I will lead the SBU effort in the tumor progression studies of URM pancreatic cancer organoid, to explore whether there are innate cell biological differences between URM and non-URM pancreatic cancer cells. For this purpose, URM pancreatic cancer organoids will be transplanted orthotopically and tumor progression will be compared to non-URM samples. I have a broad background in preclinical models of pancreatic cancer, with specific training and expertise in key research areas for this application, such as orthotopic models of PDA. We expect that the tumor progression studies will assist us with determining whether there are particular genetic contexts and signaling pathways that are different in URM pancreatic cancer compared to non-URM pancreatic cancer. They will provide another layer of information about the tumor that can be used to better characterize these URM patients. In summary, my expertise and vast experience in animal tumor models, mechanistic studies, and my record of accomplished and productive research projects in an area of highly relevance for our population, have prepared me to co-lead the proposed pilot project.

**B. Positions and Honors****Positions**

2001-2003: Doctoral Fellow, University of Buenos Aires, Argentina

2004-2007: Post-Doctoral Researcher, University of California, Davis, CA.

2007-2009: Senior Postdoctoral Associate, Stony Brook University, Stony Brook, NY.

2009- 2013: Instructor of Medicine, Stony Brook University, Stony Brook, NY.

2013- Assistant Professor, Department of Preventive Medicine, Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY

## Honors

- 2000-2001: **Carrillo-Oñativia Doctoral fellowship**. Ministry of Health, Argentina.
- 2002-2003: **Doctoral fellowship**. University of Buenos Aires, Argentina.
- 2002: **Young Investigator Award**, University of Buenos Aires, Argentina.
- 2004: **Oral presentation selected for the Young Investigator Colloquia**. 12th Biennial Meeting of the Society for Free Radical Research International SFRR 2004, Buenos Aires, Argentina, 2004
- 2004: **Marie Weldon Taubeneck Travel Award**; Department of Nutrition, University of California Davis
- 2004: **Ph.D. Thesis**: Outstanding qualification.
- 2005: **UC Davis Postdoctoral Travel Award**: To attend the Experimental Biology 2005 meeting. April 2-6, 2005. San Diego, CA, USA.
- 2006: **Marie Weldon Taubeneck Research Award** (Best 2005 paper from a Postdoctoral Researcher); Department of Nutrition, University of California Davis
- 2006-2007: **Laboratory Management Institute Award**: Laboratory Management Program for Postdoctoral Scholars, University of California, Davis.

## Professional Memberships

American Association for Cancer Research  
American Association for the Advancement of Science

## Grant Reviewer

- 2015 NIH/NCI Special Emphasis Panel ZCA1 TCRB-9 (M1); Innovative Research in Cancer Nanotechnology (IRCN); March 19-20, 2015.
- 2015 NIH/NCI Chemo/Dietary Prevention (CDP) Study Section; February 12-13, 2015.
- 2013-14 *Ad Hoc* Reviewer for University of Buenos Aires Research Grants, Buenos Aires, Argentina.
- 2013 *Ad Hoc* Reviewer for North West Cancer Research Grants, Liverpool UK.

## Manuscript Reviewer (Selected)

Gastroenterology, Cancer Prevention Research, Carcinogenesis, Free Radical Biology & Medicine, Biochemical Pharmacology, Cancer Letters, BMC Cancer, Oncology, PLoS ONE, FEBS Letters, Mitochondrion, J. Lipid Research, Biological Chemistry, Nutritional Neuroscience.

## C. Selected Peer-reviewed Publications (15 Selected from 41 peer-reviewed publications)

### Most relevant to the current application

1. **Mackenzie GG**, Bartels LE, Xie G, Papayannis I, Alston N, Vrankova K, Ouyang N and Rigas B. A novel Ras inhibitor (MDC-1016) reduces human pancreatic tumor growth in mice. *Neoplasia* **15**(10): 1184-95 (2013). PMC3819634
2. **Mackenzie GG**, Huang L, Alston N, Ouyang N, Vrankova K, Mattheolabakis G, Constantinides PP and Rigas B. (2013) Targeting Mitochondrial STAT3 with the Novel Phospho-Valproic Acid (MDC-1112) Inhibits Pancreatic Cancer Growth in Mice. *PLoS ONE* **8**(5): e61532. doi:10.1371/journal.pone.0061532. PMC3641121
3. Huang L, **Mackenzie, GG**, Sun Y, Ouyang N, Xie G, Vrankova K, Komninou, D. and Rigas B. Chemotherapeutic properties of novel phospho-nonsteroidal anti-inflammatory drugs, a new class of anticancer compounds. *Cancer Research* **71**(24):7617-27 (2011). PMC3242900
4. **Mackenzie GG**, Sun Y, Huang L, Xie G, Ouyang N, Gupta RC, Johnson F, Komninou D, Kopelovich L, and Rigas B. Phospho-Sulindac (OXT-328), a novel sulindac derivative, is safe and effective for colon cancer prevention in mice. *Gastroenterology* **139**(4):1320-32 (2010). PMC2949489. Highlighted by the editors as one in 4 out of 40 papers in the issue; in the journal's section: "This month in Gastroenterology": *Gastroenterology* 2010; **139**: 1069-1072.

**Additional recent publications of importance to the field** (in chronological order)

1. **Mackenzie GG**, Carrasquedo F, Delfino JM, Keen CL, Fraga CG, and Oteiza PI. Epicatechin, catechin and dimeric procyanidins inhibit PMA-induced NF- $\kappa$ B activation at multiple steps in Jurkat T cells. *FASEB Journal* **18**: 167-169 (2004).
2. **Mackenzie GG**, Queisser N, Wolfson M, Fraga CG, Adamo AM and Oteiza PI. Curcumin induces cell-arrest and apoptosis in association with the inhibition of constitutive active NF- $\kappa$ B and STAT3 pathways in Hodgkin's lymphoma. *International J. Cancer* **123**(1):56-65. (2008).
3. Zhao W, **Mackenzie GG**, Murray OT, Zhang Z. and Rigas B. Phosphoaspirin (MDC-43), a novel benzyl ester of aspirin, inhibits the growth of human cancer cell lines more potently than aspirin: A redox-dependent effect. *Carcinogenesis*; **30**(3):512-9 (2009). PMC2650796
4. Xie G, Sun Y, Nie T, **Mackenzie GG**, Huang L, Kopelovich L, Komninou D and Rigas B. Phospho-ibuprofen (MDC-917) is a novel agent against colon cancer: Efficacy, metabolism, pharmacokinetics and pharmacodynamics in mouse models. *The Journal of Pharmacology and Experimental Therapeutics*. Jun;**337**(3):876-886 (2011). Highlighted in the section: "*Highlighted Papers*"; *JPET* 2011; **337**: 571. PMC3101013
5. Sun Y, Huang L, **Mackenzie GG**, and Rigas, B. Oxidative stress mediates through apoptosis the anticancer effect of phospho-nonsteroidal anti-inflammatory drugs: Implications for the role of oxidative stress in the action of anticancer agents. *The Journal of Pharmacology and Experimental Therapeutics*. Sep;**338**(3):775-83 (2011). Highlighted in the section: "*Highlighted Papers*"; *JPET* 2011; **338**: 731. PMC3164348
6. **Mackenzie GG**, Ouyang N, Xie G, Vrankova K, Huang L, Sun Y, Komninou D, Kopelovich L and Rigas B. Phospho-sulindac (OXT-328) combined with difluoromethylornithine prevents colon cancer in mice. *Cancer Prevention Research*. Jul;**4**(7):1052-60 (2011). PMC3131469.
7. Xie G, Nie T, **Mackenzie GG**, Sun Y, Huang L, Ouyang N, Komninou, D., Kopelovich L, and Rigas, B. Metabolism, pharmacokinetics and pharmacodynamics of phospho-sulindac (OXT-328) and its combination with difluoromethylornithine: Inhibition of the growth of human colon cancer xenografts. *British Journal of Pharmacology*. Apr;**165**(7):2152-66 (2012). PMC3101013
8. Zhu RR, Cheng KW, **Mackenzie GG**, Huang L, Sun Y, Xie G, Vrankova K, Constantinides PP and Rigas, B. Phospho-sulindac (OXT-328) inhibits the growth of human lung cancer xenografts in mice: enhanced efficacy and mitochondria targeting by its formulation in solid lipid nanoparticles. *Pharmaceutical Research*. Nov;**29**(11):3090-101 (2012). PMC3584452
9. Huang L, Wong CC, **Mackenzie GG**, Sun Y, Cheng KW, Vrankova K, Alston N and Rigas B. Phospho-aspirin (MDC-22) inhibits breast cancer in preclinical animal models: an effect mediated by EGFR inhibition, p53 acetylation and oxidative stress. *BMC Cancer*. Feb;**28**(14):141 (2014). PMC3941604
10. Cheng KW, Wong CC, Alston N, **Mackenzie GG**, Huang L, Ouyang N, Xie G, Wiedmann T and Rigas, B. Aerosol administration of phospho-sulindac inhibits lung tumorigenesis. *Molecular Cancer Therapeutics*. Aug;**12**(8):1417-28 (2013). PMC3780561
11. Sun Y, Rowehl LM, Huang L, **Mackenzie GG**, Vrankova K, Komninou, D and Rigas, B. Phospho-ibuprofen (MDC-917) suppresses breast cancer growth: an effect controlled by the thioredoxin system. *Breast Cancer Research*. Jan 31;**14**(1):R20 (2012). PMC3496138

## **D. Research Support**

### **Current**

#### **NHI/NCI R21**

1R21CA175699-01

Mackenzie, GG (PI)

12/1/2014-11/30/2016

4.8 calendar

Title: "Pancreatic cancer control by a novel combination treatment"

The goal of this project is to investigate the anti-cancer effect of a novel farnesylthiosalicylic acid derivative in combination with a new STAT3 inhibitor as a combination approach for pancreatic cancer treatment.

#### **NHI/NCI R21**

1R21CA185209-01

Mackenzie, GG (PI)

03/09/2015-03/08/2017

3.0 calendar

Title: "Two phospho-compounds for pancreatic cancer prevention"

The goal of this project is to investigate the chemopreventive effect of two novel agents in for pancreatic cancer prevention.

#### **NIH/NCI R01**

1R01CA154172-01

7/1/2010-4/30/2015

1.2 calendar

PI: Dr. Basil Rigas Co-Investigator (Mackenzie, GG)

Title "Phospho-valproic acid for pancreatic cancer prevention"

This project evaluates the efficacy of the novel drug phospho-valproic acid in the prevention of pancreatic cancer.

#### **The Jesse and Julie Rasch Foundation**

Mackenzie, GG (PI)

12/1/2013 – 11/30/2015

1.2 calendar

Title: Evaluation of the anti-cancer efficacy of various agents against Hodgkin's Lymphoma

The major goal of this project is to evaluate the efficacy of various agents against Hodgkin's lymphoma in preclinical models.

### **Completed**

Stony Brook University-Department of Medicine

Mackenzie (PI)

12/2011-12/2012

Title: "Novel combination approach for pancreatic cancer control"

The goal of this project is to investigate the anti-cancer effect of a mechanism-based drug combination approach for pancreatic cancer

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Laura Martello-Rooney	POSITION TITLE Research Assistant Professor of Medicine		
eRA COMMONS USER NAME (credential, e.g., agency login) MARTELLOROONEY			
EDUCATION/TRAINING ( <i>Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.</i> )			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Boston University, Boston, MA	BA	09/92	Biology
Albert Einstein College of Medicine, Bronx, NY	PhD	06/01	Biological Sciences
New York University School of Medicine, NY	Postdoctoral Fellow	2002-2005	Molecular Oncology

**A. Personal Statement**

My previous backgrounds in gastrointestinal diseases and more extensively in molecular oncology have now merged in my role as Director of GI Research at SUNY Downstate Medical Center. The GI Research laboratory is focused on translational research projects with an emphasis on pancreatic cancer and a recent expansion to include colon cancer based on recent collaborations with Stony Brook University. Pancreatic and colon cancer are a primary focus due to the African American population predominant at SUNY Downstate Medical Center/Kings County Hospital Center having a higher incidence of these cancers. One current project involves generating tumor cell lines from African American patient samples in collaboration with Stony Brook University and Cold Spring Harbor Laboratory and will be crucial to understanding the disease at the molecular level. In relation to the current research proposal, I will be involved in Pilot projects 1 and 2. For Pilot project 1, I will oversee the transfer of colon tumor fixed tissue slides for miRNA profiling and colon tumor fresh tissue for the generation of novel colon cancer cell lines in addition to tumor annotation. For Pilot project 2, I will be involved in acquisition of fine-needle biopsies for the generation of pancreatic organoids.

In addition, we have projects investigating a novel drug delivery approach for pancreatic tumors utilizing the orthotopic nude mouse model, analyzing the cytokine profile of pancreatic cyst fluid and testing the radiosensitivity of pancreatic cancer cells underscoring our commitment to pursuing multiple directions in GI cancer research.

**B. Positions and Honors****Academic Positions**

1992-1996	Research Assistant, Winthrop University Hospital, Mineola, NY
2005-2008	Research Scientist, Feinstein Institute for Medical Research, Manhasset, NY
2009-	Director of GI Research, SUNY Downstate Medical Center, Brooklyn, NY
2009-	Research Assistant Professor of Medicine, SUNY Downstate Medical Center, Brooklyn, NY

**Honors**

1997-1998	Graduate Student Council Co-Chair, Albert Einstein College of Medicine
1997-2000	NIH Predoctoral Training Grant in Pharmacological Sciences, Albert Einstein College of Medicine
1999	Travel Award to AACR Special Conference, "Molecular Determinants of Sensitivity to Antitumor Agents"
2001	Bristol-Myers Squibb Scholar-In-Training Award, Annual AACR Meeting

2002-2005 NIH Postdoctoral Training Grant in Molecular Oncology and Immunology, New York University School of Medicine

## **Patent**

2003 Method for Treating Neoplasia Using Combination Chemotherapy US Patent 6,541,509

## **Certificate**

2008 Fundamentals of the Bioscience Industry Program, Stony Brook University, NY

## **Professional Memberships**

1993- American Association for the Advancement of Science  
 1999- American Association for Cancer Research  
 2003- New York Academy of Sciences  
 2010- American Gastroenterological Association

## **C. Selected Peer-reviewed Publications**

1. Hyun CS, Martello LA & Karl PI (1994) Identification of protein kinase C-alpha, epsilon, and zeta in rabbit ileal enterocytes. *Comparative Biochemistry and Physiology*, 108C: 171-178. PMID: 7981979.
2. Hyun CS, Chen CW, Shinowara NL, Palaia T, Fallick FS, Martello LA, Mueenuddin M, Donovan VM & Teichberg S (1995) Morphological factors influencing transepithelial conductance in a rabbit model of ileitis. *Gastroenterology*, 109: 13-23. PMID: 7797012.  
<http://www.sciencedirect.com/science/article/pii/S0016508595902643>
3. Homaidan FR, Martello LA, Melson SJ & Burakoff R (1998) Regulation of electrolyte transport by nitric oxide in the mouse cecum. *European Journal of Pharmacology*, 350: 93-99. PMID: 9683020.  
<http://www.sciencedirect.com/science/article/pii/S0014299998002210>
4. Martello LA, McDaid HM, Regl D, Yang C-PH, Meng D, Pettus TRR, Kaufman MD, Arimoto H, Danishefsky SJ, Smith AB III & Horwitz SB (2000) Taxol and discodermolide represent a synergistic drug combination in human carcinoma cell lines. *Clinical Cancer Research*, 6: 1978-1987. PMID: 10815923.  
<http://clincancerres.aacrjournals.org/content/6/5/1978.long>
5. Goncalves A, Braguer D, Kamath K, Martello L, Briand C, Horwitz S, Wilson L & Jordan MA (2001) Resistance to Taxol in lung cancer cells associated with increased microtubule dynamics. *Proceedings of the National Academy of Sciences USA*, 98: 11737-11742. PMCID: PMC58799
6. Martello LA, LaMarche MJ, He L, Beauchamp TJ, Smith AB III & Horwitz SB (2001) The relationship between Taxol and (+)-discodermolide: synthetic analogs and modeling studies. *Chemistry & Biology*, 8: 843-855. PMID: 11564553. <http://www.sciencedirect.com/science/article/pii/S1074552101000552>
7. Martello LA, Verdier-Pinard P, Shen H-J, He L, Torres K, Orr GA & Horwitz SB (2003) Elevated levels of microtubule destabilizing factors in a Taxol-resistant/dependent A549 cell line with an alpha-tubulin mutation. *Cancer Research*, 63: 1207-1213. PMID: 12649178.  
<http://cancerres.aacrjournals.org/content/63/6/1207.long>
8. Verdier-Pinard P, Wang F, Martello L, Burd B, Orr GA & Horwitz SB (2003) Analysis of tubulin isotypes and mutations from taxol-resistant cells by combined isoelectrofocusing and mass spectrometry. *Biochemistry*, 42: 5349-5357. PMID: 12731876. <http://pubs.acs.org/doi/abs/10.1021/bi027293>
9. Martello LA & Pellicer A (2006) Biochemical and biological analyses of the Rgr RalGEF oncogene. *Methods in Enzymology*, 407: 115-128. PMID: 16757319.  
<http://www.sciencedirect.com/science/article/pii/S0076687905070114>
10. Osei-Sarfo K, Martello L, Ibrahim S, & Pellicer A (2011) The human Rgr oncogene is overexpressed in T-cell malignancies and induces transformation by acting as a GEF for Ras and Ral. *Oncogene*, 30: 3661-3671. PMCID: PMC3126870
11. Martello LA, Wadgaonkar R, Gupta R, Machado F, Mascareno E, Tanowitz HB and Haseeb MA. (2013) Characterization of *Trypanosoma cruzi* Infectivity, Proliferation and Cytokine Patterns in Gut and Pancreatic Epithelial Cells Maintained *In Vitro*. *Parasitology Research*, 112(12): 4177-4183. PMID: 24018709. <http://link.springer.com/article/10.1007%2Fs00436-013-3609-7>

12. Burkhart C, Fleishman D, Kohn R, Commane M, Garrigan J, Kurbatov V, Toshkov I, Ramachandran R, Martello L, Gurova KV. (2014) Curaxin CBL0137 eradicates drug resistant cancer stem cells and potentiates efficacy of gemcitabine in preclinical models of pancreatic cancer. *Oncotarget*, 5(22): 11038-11053. PMCID: PMC4294371

## **D. Research Support**

### **Pending Research Support**

SUNY Health Network of Excellence Collaboration Grant

SUNY partnership to study racial ethnic differences in GI cancer biology

The goal of this project is to build a collaborative partnership between two SUNY major universities, Stony Brook University and Downstate Medical Center, and the NCI-designated Cancer Center at Cold Spring Harbor Laboratory focused on studying racial ethnic differences in GI cancer biology using advanced technologies.

Role: Co-Investigator (PI: M. Salifu (Downstate), E. Li (Stony Brook), W. McCombie (CSHL))

NIH P20 Feasibility Studies to Build Collaborative Partnerships in Cancer Research (PAR-14-152)

Partnership to study racial/ethnic differences in GI cancer biology

The goal of this proposal is to build on existing SUNY relationships and expand the team to include Cold Spring Harbor Laboratory with the main focus of examining racial/ethnic differences in GI cancer biology, specifically colon and pancreatic cancer, as a pathway to impacting cancer disparities.

Role: Co-Investigator (PI: M. Salifu (Downstate), E. Li (Stony Brook), W. McCombie (CSHL))

### **Completed Research Support**

Research Agreement, Buffalo BioLabs

11/2013-8/2014

Evaluation of a novel anticancer agent in a mouse model of pancreatic cancer.

The goal of this project is to test the efficacy of a novel anticancer agent using an orthotopic mouse model of pancreatic cancer.

Role: PI

Investigator Sponsored Trial, Shire Pharmaceuticals

8/2010-8/2013

Gene expression in ulcerative colitis: a pilot study

The goal of this project is to identify ulcerative colitis specific genes using peripheral blood mononuclear cells and colonic tissue that may be used as prognostic biomarkers of disease.

Role: PI

Dean's Initiative in Research Award, SUNY Downstate Medical Center

4/2012-4/2013

Characterization of *Trypanosoma cruzi* Infectivity, Proliferation and Cytokine Patterns in Gut and Pancreatic Epithelial Cells Maintained *In Vitro*.

The goal of this project is to examine the in vitro infectivity of colon and pancreatic epithelial cells and its effects on cell proliferation and cytokine production.

Role: Co-Investigator (PI: H. Siddiqi)

Dean's Initiative in Research Award, SUNY Downstate Medical Center

4/2011-8/2012

Drug-eluting microparticles for the treatment of pancreatic cancer (pilot project)

The goal of this project is to compare the effectiveness of drug-eluting microparticles to systemic drug when injected into the pancreas of an orthotopic nude mouse model of pancreatic cancer.

Role: Co-Investigator (PI: F. Gress)

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Moro O. Salifu</b>	POSITION TITLE <b>Professor of Medicine, Chair of Medicine, Chief of Nephrology</b>		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>morosalifu</b>			
EDUCATION/TRAINING ( <i>Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.</i> )			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Dokuz Eylul University Medical Sch., Turkey	MD	1994	Medicine
SUNY Downstate Medical Center, Brooklyn, NY	MPH	2004	Public Health
George Washington University, DC	MBA	2008	Health Care Business

**A. Personal Statement**

In my capacity as PI and Director of the NIH funded Brooklyn Health Disparities Center (BHDC), I promote health disparities research in all fields and foster collaborations between stakeholders that will result in research addressing health disparities. The work proposed by Dr Li is a novel initiative to increase representation of GI biospecimens collected from underserved populations, and to increase under-represented minorities (URM) for training in translational research. BHDC also is a collaborative effort between the Brooklyn Borough Presidents Office and the Arthur Ashe Institute for Urban Health. These experiences will be useful in providing the necessary administrative oversight needed for the conduct of the proposal. Furthermore, I am the Chair of Medicine directing research and training of faculty and house staff at Downstate. These positions also will help leverage resources to meet the needs of this proposal.

**B. Positions and Honors**

1995 - 1998	Internship and Residency, SUNY Downstate Medical Center, Department of Medicine, Brooklyn, NY
1998 - 2000	Nephrology Fellowship & Chief Fellow, SUNY Downstate Medical Center, Department of Medicine, Brooklyn, NY
2000 - 2001	Fellowship in Transplant Nephrology, SUNY Downstate Medical Center, Department of Medicine, Brooklyn, NY
2001 - 2005	Assistant Professor of Medicine, SUNY Downstate Medical Center, Brooklyn, NY
2003 - Present	Program Director, Nephrology Fellowship Program, SUNY Downstate Medical Center, Brooklyn, NY
2005 - 2008	Associate Professor of Medicine, SUNY Downstate Medical Center, Brooklyn, NY
2008 - Present	Professor and Chief, Division of Nephrology and Director Transplant Program, Department of Medicine, SUNY Downstate Medical Center, Brooklyn, NY
Jan – Jun 2013	Interim Chair, Dept of Medicine, SUNY Downstate Medical Center, Brooklyn, NY
Jul 2013 - Pres	Professor and Chair, Dept of Medicine, SUNY Downstate Medical Center, Brooklyn, NY

**Awards**

1996 - 2001	First Place Award, Housestaff Basic Science Research, SUNY Downstate Medical Center, Brooklyn, NY
2003 - 2004	Outstanding Teacher of the Year Award, Department of Medicine, SUNY Downstate Medical Center, Brooklyn, NY
2004 - 2005	Outstanding Educator of the Year Award, Division of Nephrology, SUNY Downstate Medical Center, Brooklyn, NY

- 2010 Special Recognition of valuable contribution to Transplant Program, SUNY Downstate Medical center
- Oct 2013 Kings of Kings County Award for outstanding contributions to medicine in Brooklyn

### Committees

- 2004 - Present Member of the Medical Board, New York Organ Donor Network
- 2005 - 2007 New York State (Region 9) Representative to the United Network for Organ Sharing (UNOS) Minority Affairs Committee
- 2011 - Present: Chair of the Executive Committee, BHDC

### Professional Membership

- 1998 - Present American College of Physicians
- 2002 - Present American Society of Nephrology

## C. Selected Peer-reviewed Publications

1. Mallappallil M, Friedman EA, Delano BG, McFarlane SI, Salifu MO. Chronic kidney disease in the elderly: evaluation and management. Clin Pract (Lond). 2014;11(5):525-535.
2. Brar A, Babakhani A, Salifu MO, Jindal RM. Evaluation of non-adherence in patients undergoing dialysis and kidney transplantation: United States transplantation practice patterns survey. Transplant Proc. 2014 Jun;46(5):1340-6.
3. Babinska A1, Clement CC, Swiatkowska M, Szymanski J, Shon A, Ehrlich YH, Kornecki E, Salifu MO. Development of new anti-atherosclerotic and anti-thrombotic drugs utilizing F11 receptor (F11R/JAM-A) peptides. Biopolymers. 2014 Apr;101(4):322-34
4. Brar A, Babakhani A, Salifu MO, Jindal RM. Evaluation of non-adherence in patients undergoing dialysis and kidney transplantation: United States transplantation practice patterns survey. Transplant Proc. 2014 Jun;46(5):1340-6.
5. Brar A, Babakhani A, Salifu MO, Jindal RM. Evaluation of Non-adherence in Patients Undergoing Dialysis and Kidney Transplantation: United States Transplantation Practice Patterns Survey. Transplant Proc. S0041-1345(14)00135-3, 2014 [Epub ahead of print]
6. Brar A, Jindal RM, Elster EA, Tedla F, John D, Sumrani N, Salifu MO. Effect of peripheral vascular disease on kidney allograft outcomes: a study of U.S. Renal data system. Transplantation. 2013 95(6):810-5.
7. Norin AJ, Mondragon-Escorpizo MO, Brar A, Hochman D, Sumrani N, Distant DA, Salifu MO. Poor kidney allograft survival associated with positive B cell - Only flow cytometry cross matches: a ten year single center study. Hum Immunol. 2013; 74(10):1304-12. PMID: 23811689.  
<http://www.sciencedirect.com/science/article/pii/S0198885913001845>
8. Brar A, Jindal RM, Sumrani N, John D, Mondal Z, Tedla F, Salifu MO. Impact of Renal Posttransplantation Amputation on Allograft Outcomes: A Study of United States Renal Data System. Transplantation. 2013; 95(10):1249-53. PMID: 23591760.  
<http://journals.lww.com/transplantjournal/pages/articleviewer.aspx?year=2013&issue=05270&article=00010&type=abstract>
9. Brar A, Jindal RM, Elster EA, Tedla F, John D, Sumrani N, Salifu MO. Effect of peripheral vascular disease on kidney allograft outcomes: a study of U.S. Renal data system. Transplantation. 2013; 95(6):810-5. PMID: 23354295.  
<http://journals.lww.com/transplantjournal/pages/articleviewer.aspx?year=2013&issue=03270&article=00005&type=abstract>
10. Brown TS, Elster EA, Stevens K, Graybill JC, Gillern S, Phinney S, Salifu MO, Jindal RM. Bayesian modeling of pretransplant variables accurately predicts kidney graft survival. Am J Nephrol. 2012; 36(6):561-9. PMID: 23221105. <http://www.karger.com/Article/FullText/345552>
11. Brar A, Jindal RM, Abbott KC, Hurst FP, Salifu MO. Practice patterns in evaluation of living kidney donors in United Network for Organ Sharing-approved kidney transplant centers. Am J Nephrol. 2012; 35(5):466-73. PMID: 22555113. <http://www.karger.com/Article/FullText/338450>
12. Karabicak I, Aytug S, Lewis S, Shah S, Sumrani N, Hayat A, Distant DA, Salifu MO. Long-term kidney transplant outcome in obese patients in a predominantly African American population. Clin Transplant. 2011; 25(3):E264-70. PMID: 21332793. <http://onlinelibrary.wiley.com/doi/10.1111/j.1399-0012.2011.01412.x/abstract;jsessionid=2C2964202D112699C6D2CD90745A5A48.f04t03>

13. Azari BM, Marmur JD, Salifu MO, Cavusoglu E, Ehrlich YH, Kornecki E and Babinska A. Silencing of the F11R gene reveals a role for F11R/JAM-A in the migration of inflamed vascular smooth muscle cells and in atherosclerosis. *Atherosclerosis* 2010; 212:197-205. PMID: 20627246. <http://www.sciencedirect.com/science/article/pii/S0021915010003928>
14. Salifu MO, Abbott KC, Aytug S, Hayat A, Hara DM, Shah S, Friedman EA, Delano BG, McFarlane SI, Hurst FP, Flom PL, Jindal RM. New-onset diabetes after hemodialysis initiation: impact on survival. *Am J Nephrol*. 2010; 31(3):239-46. PMID: 20068288. <http://www.karger.com/Article/FullText/276542>
15. Salifu MO, Shah S, Iqbal MH, Nabi M, Hayat A, Whaley-Connell AT, Sowers JR, McFarlane SI: Effect of Ethnicity on the Progression of Diabetic Kidney Disease Independent of Glycemic Control. *Am J Nephrol* 2009; 30:261-267. PMID: 19494485. <http://www.karger.com/Article/FullText/223527>
16. Ong KL, Leung RYH, Babinska A, Salifu OM, Ehrlich YH, Kornecki E, Wong YFL, Tso WKA, Cherny SS, Sham PC, Lam TH, Lam SLK, Cheung MYB. Elevated plasma level of soluble F11 Receptor/Junctional Adhesion Molecule-A (F11R/JAM-A) in Hypertension. *American Journal of Hypertension* 2009; 22(5):500-05. PMID: 19214165. <http://ajh.oxfordjournals.org/content/22/5/500.long>

## D. Research Support

### Ongoing Research Support

NIH 1 P20MD00687501 Salifu, M (PI) 06/14/2012 – 01/31/2017  
Brooklyn Health Disparities Center (BHDC)

The overall goal of BHDC is to foster community engaged participatory research, training and intervention toward the reduction of health disparities in Brooklyn, New York and to disseminate evidence-based health findings among academic, community, and policy stakeholders.

Role: PI

NIH 1 R03-CA165139-01A1 Rosalind Ramsey Goldman (PI)

Cancer risk after renal transplant in autoimmune disease using the United States Renal Data System.

Role: Co-Investigator

Institutional Support Grant (SUNY) # 921372-15 Salifu, M (PI) 8/2009-6/2013

Role of the F11 receptor (F11R) in atherosclerosis.

The goal of this study is to determine the effect of F11R peptide inhibitors on atherosclerosis development.

Role: PI

### Completed Research Support

NIH 1 R43 HL103037-01 Olson (PI)/Provid NJ; Kornecki (PI)/SUNY NY 05/01/2010 – 04/30/2012  
F11R antagonists for atherosclerosis

The goal of this study is to identify new potent inhibitor (peptide mimetics) of platelet aggregation and adhesion to inflamed endothelium via blockade of the F11R-F11R interaction for prevention and treatment of atherosclerosis.

Role: Co-Investigator

J. G. Bhat Foundation Award # 55136 Salifu, M (PI) 8/2010-7/2013

Effect of erythropoietin on platelet function

The goal of this study is to determine the effect of erythropoietin on platelet function and its impact on cardiovascular disease in patients with kidney disease.

Role: PI

Program Director/Principal Investigator (Last, First, Middle): Saltz, Joel H.

**BIOGRAPHICAL SKETCH**

NAME Joel H. Saltz, MD, Ph.D	POSITION TITLE Cherith Endowed Chair of Biomedical Informatics, Associate Director of the Stony Brook Cancer Center and VP for Clinical Informatics		
eRA COMMONS USER NAME (credential, e.g., agency login) JOELHSALTZ			
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	BS	Dec 1977	Mathematics, Physics
University of Michigan, Ann Arbor, MI	MS	Dec 1978	Mathematics
Duke University, Durham, NC	MD	Sep 1985	MSTP Program
Duke University, Durham, NC	PhD	Sep 1985	MSTP Program
Johns Hopkins Medical Institutions, Baltimore, MD	Residency	Jul 1996 - Jun 1998	Clinical Pathology, Pathology Informatics

**A. Personal Statement**

I am dedicated to the development of principles, techniques and tools that can be used by cancer researchers to assemble a coherent biomedical picture by integrating information from multiple complementary microscopy, Radiology imaging and molecular data sources to better understand cancer invasion, heterogeneity, metastasis and microenvironment and to develop and coordinate cancer therapies, predict outcome and response to treatments, generate basic insights into pathophysiology, and identify new treatment targets. My approach consists of closely coordinated efforts in image analysis, machine learning, database design and high end computing. I have spearheaded a variety of multi-disciplinary efforts that have led to the development of innovative tools and middleware components for the management, analysis, and integration of heterogeneous biomedical data. This project extends and leverages tools and methods I developed through years of funded projects supported by a wide range of institutes and agencies including NCI, NLM, NIBIB, NSF, DARPA, AFOSR, NASA, DOD and DOE to develop innovative techniques, methodologies, algorithms and software systems to support integrative data analyses, large scale digital microscopy, high-performance computing, data management, and data federation and have a long track record of managing substantial research and development enterprises. My research interests encompass linking tissue derived morphology to “-omics”, treatment response and outcome in melanoma, colorectal and GI cancer, investigating cancer systems biology, underlying cancer initiation, invasion and metastasis in animal and neurosphere models, to studies that link Radiology, Pathology and “-omics”. I served as PI of a P20 NIBIB funded BISTI center dedicated to integrative Pathology and Radiology image analysis, as Program Director of the Emory In Silico Research Center for Excellence, and led the Biomedical Informatics Programs in both Ohio State and the Emory CTSA. In September 2013, I became the Associate Director for Informatics for the Stony Brook Cancer Center with the goal of developing a thematic area that focuses on development of methods to generate and analyze integrative multi-scale, morphological/molecular cancer tissue characterizations and use of integrated characterizations to 1) better understand tumor stroma interactions, multi-clonality and tumor heterogeneity; 2) develop methods to leverage heterogeneity information for treatment planning and; 3) to better monitor and steer cancer treatments.

**B. Positions and Honors**

- 1985-1986 Staff Scientist, Institute for Computer Applications in Science and Engineering (ICASE), NASA Langley Research Center, Hampton, VA
- 1986-1989 Assistant Professor, Department of Computer Science, Yale University, New Haven, CT
- 1989-1992 Lead Computer Scientist, Institute for Computer Applications in Science and Engineering (ICASE), NASA Langley Research Center, Hampton, VA
- 1992-1997 Associate Professor, Department of Computer Science and Institute for Advanced Computer Studies, University of Maryland, College Park, MD
- 1997-1998 Associate Professor, Department of Pathology, The Johns Hopkins Medical Institutions, Johns Hopkins University, Baltimore, MD

Program Director/Principal Investigator (Last, First, Middle): Saltz, Joel H.

- 1997-2001 Professor, Department of Computer Science and Institute for Advanced Computer Studies, University of Maryland, College Park, MD
- 1998-2001 Professor, Department of Pathology, The Johns Hopkins Medical Institutions, The Johns Hopkins University, Baltimore, MD
- 1998-2001 Director, Informatics Division, Department of Pathology, The Johns Hopkins Medical Institutions, The Johns Hopkins University, Baltimore, MD
- 2001-2008 Professor and Chair, Department of Biomedical Informatics, College of Medicine and Public Health, The Ohio State University, Columbus, OH
- 2001-2008 Professor, Dept. of Computer and Information Science, The Ohio State University, Columbus
- 2002-2008 Professor and Vice Chair, Department of Pathology, The Ohio State University, Columbus, OH
- 2004-2008 Endowed Chair, Dorothy M. Davis Cancer Fund, Arthur G. James Cancer Hospital, The Ohio State University
- 2008- 2013 Director, Center for Comprehensive Informatics, Emory University, Atlanta, GA
- 2008- 2013 Professor, Department of Pathology, Mathematics and Computer Science, Biostatistics and Bioinformatics, School of Medicine, Emory University, Atlanta, GA
- 2009-2013 Adjunct Professor, School of Computer Science, School of Computational Science and Engineering, College of Computing, Georgia Institute of Technology, Atlanta, GA
- 2011-2013 Professor and Chair, Department of Biomedical Informatics, Emory University, Atlanta, GA
- 2013- Cherith Endowed Professor and Chair, Department of Biomedical Informatics, Stony Brook University, Stony Brook NY
- 2013- Professor of Radiology, Pathology and Computer Science, Stony Brook University, Stony Brook NY
- 2013- Associate Director Cancer Center, Stony Brook University Cancer Center, Stony Brook NY
- 2013- Vice President for Clinical Informatics, Stony Brook Medicine, Stony Brook NY

#### **Other Experience and Professional Memberships**

- 1997-2004 Programming Tools and Environments area leader and executive committee member for NSF-funded National Partnership for Advanced Computational Infrastructure (NPACI)
- 1999-2002 Founding Member and Secretary-Treasurer of the Association for Pathology Informatics
- 2001 Board Certified, Clinical Pathology
- 2004-2006 Member, NLM BLIRC, NIH Human Brain Study Section (ZRG1 MDCNG 55), National Centers for Biomedical Computing Special Emphasis Review Panel; ACRIN Special Emphasis Panel ZCA1 SRRB-9 (O1) R and multiple other ad-hoc NIH study sections
- 2006-2010 Biomedical Library and Informatics Review Committee (BLIRC), National Institute of Health (NIH)/National Library of Medicine (NLM)
- 2002-present Fellow, College of American Pathologists
- 2009-present Fellow, American College of Medical Informatics
- 2009-present Member, External Advisory Committee, NHLBI Pediatric Cardiac Translational Research Program, titled "Bench to Bassinet"
- Member, IEEE, ACM, AMA, AMIA, CAP

#### **C. Selected Peer-reviewed Publications (*selected from >170*)**

##### **Most relevant to the current application**

1. Post AR, Kurc T, Cholleti S, Gao J, Lin X, Bornstein W, Cantrell D, Levine D, Hohmann S, Saltz JH. The Analytic Information Warehouse (AIW): a platform for analytics using electronic health record data. J Biomed Inform. 2013 Jun;46(3):410-24. doi: 10.1016/j.jbi.2013.01.005. Epub 2013 Feb 9. PubMed PMID: 23402960; PubMed Central PMCID: PMC3660520.
2. Hersh WR, Weiner MG, Embi PJ, Logan JR, Payne PR, Bernstam EV, Lehmann HP, Hripcsak G, Hartzog TH, Cimino JJ, Saltz JH. Caveats for the use of operational electronic health record data in comparative effectiveness research. Med Care. 2013 Aug;51(8 Suppl 3):S30-7. doi: 10.1097/MLR.0b013e31829b1dbd. PubMed PMID: 23774517; PubMed Central PMCID: PMC3748381.
3. Cholleti S, Post A, Gao J, Lin X, Bornstein W, Cantrell D, Saltz J. Leveraging derived data elements in data analytic models for understanding and predicting hospital readmissions. AMIA Annu Symp Proc.

Program Director/Principal Investigator (Last, First, Middle): Saltz, Joel H.

2012;2012:103-11. Epub 2012 Nov 3. PubMed PMID: 23304278; PubMed Central PMCID: PMC3540449.

4. Cooper LA, Kong J, Gutman DA, Wang F, Gao J, Appin C, Cholleti S, Pan T, Sharma A, Scarpance L, Mikkelsen T, Kurc T, Moreno CS, Brat DJ, Saltz JH. Integrated morphologic analysis for the identification and characterization of disease subtypes. *J Am Med Inform Assoc.* 2012 Mar-Apr;19(2):317-23. doi: 10.1136/amiajnl-2011-000700. Epub 2012 Jan 24. PubMed PMID: 22278382; PubMed Central PMCID: PMC3277636.
5. Kong J, Cooper LA, Wang F, Gao J, Teodoro G, Scarpance L, Mikkelsen T, Schniederjan MJ, Moreno CS, Saltz JH, Brat DJ. Machine-based morphologic analysis of glioblastoma using whole-slide pathology images uncovers clinically relevant molecular correlates. *PLoS One.* 2013 Nov 13;8(11):e81049. doi: 10.1371/journal.pone.0081049. eCollection 2013. PubMed PMID: 24236209; PubMed Central PMCID: PMC3827469.

#### **Additional recent publications of importance to the field (in chronological order).**

1. Post AR, Kurc T, Rathod H, Agravat S, Mansour M, Torian W, Saltz JH. Semantic ETL into i2b2 with Eureka! AMIA Jt Summits Transl Sci Proc. 2013 Mar 18;2013:203-7. eCollection 2013. PubMed PMID: 24303265; PubMed Central PMCID: PMC3845783.
2. Brown J, Ahamad M, Ahmed M, Blough DM, Kurc T, Post A, Saltz J. Redactable and auditable data access for bioinformatics research. AMIA Jt Summits Transl Sci Proc. 2013 Mar 18;2013:21-5. eCollection 2013. PubMed PMID: 24303231; PubMed Central PMCID: PMC3845775.
3. Kim M, Kurc T, Orso A, Cobb J, Gutman D, Harrold MJ, Post A, Sharma A, Saltz J. An informatics framework for testing data integrity and correctness of federated biomedical databases. AMIA Jt Summits Transl Sci Proc. 2011;2011:22-6. Epub 2011 Mar 7. PubMed PMID: 22211176; PubMed Central PMCID: PMC3248750.
4. Cooper LA, Gutman DA, Chisolm C, Appin C, Kong J, Rong Y, Kurc T, Van Meir EG, Saltz JH, Moreno CS, Brat DJ. The tumor microenvironment strongly impacts master transcriptional regulators and gene expression class of glioblastoma. *Am J Pathol.* 2012 May;180(5):2108-19. doi: 10.1016/j.ajpath.2012.01.040. Epub 2012 Mar 20. PubMed PMID: 22440258; PubMed Central PMCID: PMC3354586.
5. Kong J, Cooper LA, Wang F, Gao J, Teodoro G, Scarpance L, Mikkelsen T, Schniederjan MJ, Moreno CS, Saltz JH, Brat DJ. Machine-based morphologic analysis of glioblastoma using whole-slide pathology images uncovers clinically relevant molecular correlates. *PLoS One.* 2013 Nov 13;8(11):e81049. doi:10.1371/journal.pone.0081049. eCollection 2013. PubMed PMID: 24236209; PubMed Central PMCID: PMC3827469.

#### **D. Research Support**

##### **Active**

R01LM011119 (PI: Saltz)

07/01/2011–05/31/2015

NLM/NIH

Role: PI

*Informatics for Integrative Brain Tumor Whole Slide Analysis:* This project will develop methods, analytic pipelines, and data management tools that will make it feasible to systematically carry out large-scale comparative analyses of brain tumor histological features and of patterns of protein and gene expression. A data repository populated with images, features, and analytic results will be deployed from the project that will provide a publicly available resource for brain tumor research.

R01LM009239 (PIs: Foran/Saltz)

09/01/2013-08/31/2017

NCI/NLM

Role: Dual PI

*Image Mining for Comparative Analysis of Expression Patterns in Tissue Microarray:* This project's aims are: (1) Develop and evaluate a new family of multi-stage, searching algorithms to facilitate quick, reliable interrogation of large-scale, clinical and research, microscopy applications including whole-slide imaging and tissue microarray; (2) Develop and evaluate a suite of high-throughput services capable of automatically detecting, archiving and indexing user-specified objects (e.g. tissues, cells) in large collections of images and implement extensions to the data models and support for optimized pipeline selection.

Program Director/Principal Investigator (Last, First, Middle): Saltz, Joel H.

1U24CA80924

09/01/2014-08/31/2019

NCI

Role: PI

*Tools to Analyze Morphology and Spatially Mapped Molecular Data:* This project is to develop, deploy, and disseminate a suite of open source tools and integrated informatics platform that will facilitate multi-scale, correlative analyses of high resolution whole slide tissue image data, spatially mapped genetics and molecular data for cancer research.

Emory University

07/24/2014-10/31/2015

NCI

Role: Site PI

*caMicroscope-A Digital Pathology Integrative Query System.* This project will address the interoperability for digital pathology data, improve integration and analytic capabilities between The Cancer Genome Atlas (TCGA) and The Cancer Imaging Archive (TCIA), and raise the level of interoperability to create the foundation required for pilot demonstration projects in each of the targeted research domains: clinical imaging, pre-clinical imaging, and digital pathology imaging.

SUNY Networks of Excellence

07/01/2014-06/30/2015

Corporate Funded

Role: Thrust Area T4 Project Leader

*Excellence in Materials and Advanced Manufacturing: Biomaterials.* This project is focused on biomaterials as a technology that can be applied to pre-disease and post-disease patient conditions.

**Completed**

UL1TR000454 (PI: Stephens)

09/17/2007-05/31/2017\*

NIH

Role: Program Director, Biomedical Informatics Program

*Atlanta Clinical and Translational Science Institute:* The Atlanta Clinical and Translational Science Institute is an inter-institutional magnet that concentrates basic, translational, and clinical investigators, community clinicians, professional societies, and industry collaborators in dynamic clinical and translational research projects. *\*Program Director moved to another institution 9/2013.*

GCC Award (PI: Saltz)

07/01/2009-06/30/2014\*

*Georgia Cancer Coalition - Distinguished Cancer Clinician and Scientist Program:* The goal of this program is to develop a robust, statewide group of leading and nationally-renowned cancer clinicians and scientists who are engaged in the most promising areas of cancer research, prevention, and treatment. *\*PI moved to another institution 9/2013.*

12ST1100 (PD: Saltz; PI: Brat)

10/31/2012-09/30/2013

SAIC-F/NCI

Role: Director

*In Silico Research Center for Excellence (Extension):* This research conducts integrative in silico experiments leveraging complementary molecular, pathology and radiology brain tumor data obtained in The Cancer Genome Atlas (TCGA), Rembrandt, and Vasari studies.

A10-0064-S006 (PI: Saltz)

04/01/2012-09/30/2013

Univ of Tennessee-Knoxville

Role: PI

*Integrative Analysis of Brain Tumors using High-Resolution Microscopy Imaging:* In the proposed project, we will port the analysis pipelines and tools that we have developed to the Nautilus system and carry out remote analyses for the characterization of brain tumor morphology using large whole slide image datasets.

29XS193 (PD: Saltz; PI: Brat)

08/24/2009-08/23/2012

SAIC-F/NCI

Role: Director

*In Silico Research Center for Excellence:* This research conducts integrative in silico experiments leveraging complementary molecular, pathology and radiology brain tumor data obtained in The Cancer Genome Atlas (TCGA), Rembrandt, and Vasari studies.

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Yalini Senathirajah	POSITION TITLE Assistant Professor		
eRA COMMONS USER NAME (credential, e.g., agency login) YSENATH			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Harvard University, Boston MA	AB	06/79	Biology
Ontario Veterinary College, Ontario CA			Veterinary Medicine
Columbia University, New York NY (NLM Predoctoral Fellow, CDC-funded public health informatics leadership track)	PhD	10/10	Biomedical Informatics

### A. Personal statement

I have a recent PhD in Biomedical Informatics from Columbia, with dissertation on novel approaches to electronic health record design. Work as webmaster of Columbia University Health Sciences campus involved extensive experience in creation of data-base driven applications for research. I assisted in the HITEC evaluation of NYS RHIOs, and various other public health informatics projects with large datasets including an analysis of NYC immunization registry data showing that EHR automated reporting had beneficial effects on various measures. I worked with the large clinical data repository and warehouses at Columbia/NYP, which have an architecture well suited to integration of heterogeneous information sources from multiple systems. My research also involved work on how to present such data in ways that decrease the cognitive load of the user and facilitate research. I am familiar with issues in colorectal cancer and other types of screening in underserved communities due to work with Dr. Sherri Sheinfeld-Gorin in creating online tools to education primary care providers in how to talk to patients about colorectal cancer screening, with decision support. Similar projects included online tools for prostate cancer and HIV pre-screening in these populations. I have additional formal training in mHealth research and 'Big data' analytics techniques via NIH institutes.

### B. Positions and Honors:

8/2011 - present Assistant Professor, Dept. of Medical Informatics, SUNY Downstate Medical Center, NY  
 2010-2011 Instructor/Researcher, Department of Biomedical Informatics, Columbia University, NY  
 2006-2010 NLM Pre-doctoral Fellow, Dept. of Biomedical Informatics, Columbia University, NY  
 2004-2005 Programmer/Researcher, Harlem Health Promotion Center, Columbia University, NY  
 2003-2004 Webmaster, Columbia School of Journalism, NY  
 1998-2003 Webmaster, Health Sciences Campus, Columbia Medical Center, NY

### Other Experience and Professional Memberships

2005- Member and peer reviewer, American Medical Informatics Association  
 2010- Member, Health Information Management Systems Society (HIMSS) Usability Task Force  
 2005-2010 Member, Association for Computing Machinery  
 2005-2008 Member, American Public Health Association

### Honors

2014 **Finalist, AMIA 'Ideas that Work' iHealth International Innovation Competition**  
 2013 **Best paper award**, Context-sensitive Health Informatics Conference; *'Essential Questions: Accuracy, Errors and User Perceptions in a User-configurable Electronic Health Record'*  
 2010 **Invited Speaker**, Danish National Health Information Technology conference  
 2009 **Best poster award**, National Library of Medicine Informatics Trainee Conference,  
 2009 *Development and Evaluation of a web 2.0- based EHR*

2009 **Best talk award**, Robert Wood Johnson public health informatics fellows meeting, 2009: *Rapid reconfiguration of a web 2.0- based EHR to meet an emerging need (H1N1)*.  
2006 **Finalist, Diana Forsythe Award** for best qualitative-methods paper in 2006. AMIA 2006. *Health Information Seeking and Technology Use in Harlem – A Pilot Study Using Community- Based Participatory Research*

**Memberships:** American Medical Informatics Association (AMIA), Health Information Management Systems Society (HIMSS), Association of Computing Machinery (ACM)

**C. Selected Peer-reviewed Publications** (selected from 21 peer-reviewed publications)  
**5 most relevant to the current application:**

Merrill J, Phillips A, Keeling J, Kaushal R, Senathirajah Y. **Effects of automated immunization registry reporting via an electronic health record deployed in community practice settings.** Appl Clin Inform. 2013 Jun 12;4(2):267-75.

**Visual Clustering Analysis of CIS Logfiles to Inform Creation of a User-configurable Web 2.0 CIS Interface.** Methods of Information in Medicine, 2011.

**Important ingredients for health adaptive information systems.** Senathirajah Y, Bakken S. Stud Health Technol Inform 169():280-4 (2011) PMID 21893757

**Architectural and usability considerations in the development of a web 2.0-based EHR.** Senathirajah Y, Bakken S. Stud Health Technol Inform. 2009;143:315-21.

**Additional recent publications of importance to the field (in chronological order)**

**The Clinician in the Driver's Seat: Part 1 - A User-composable Electronic Health Record Platform.**

Senathirajah Y, Kaufman, D, Bakken S. Journal of Biomedical Informatics, Nov/Dec 2014  
doi:10.1016/j.jbi.2014.09.002.

**Part 2 - Intelligent Uses of Space in a Drag/drop User-composable Electronic Health Record.**

Senathirajah Y, Kaufman, D, Bakken S. Journal of Biomedical Informatics, Nov/Dec 2014 (available online).

**Cognitive analysis of a highly configurable web 2.0 EHR interface.** Senathirajah Y, Kaufman, D., Bakken S. Paper, AMIA Annu Symp Proc. 2010:732-736.

**Logfile analysis of CIS use to inform creation of a user-configurable widget-based web 2.0 CIS interface: a feasibility study.** Senathirajah Y, Bakken S. Paper, AMIA Annu Symp Proc. 2009.

**Health information seeking and technology use in Harlem - a pilot study using community-based participatory research.** Senathirajah Y, Kukafka R, Guptarak M, Cohall A.  
AMIA Annu Symp Proc. 2006:704-8. PMID: 17238432

**Systematic development and usability testing of a physician-based prostate cancer education program in an African American community.** Sheinfeld Gorin S, Franco R, Hajiani F, Senathirajah Y. AMIA Annu Symp Proc. 2007 Oct 11:1112. PMID: 18694209

**Feasibility of using computer-assisted interviewing to enhance HIV test counseling in community settings.** Cohall AT, Dini S, Senathirajah Y, Nye A, Neu N, Powell D, Powell B, Hyden C. Public Health Rep. 2008 Nov-Dec;123 Suppl 3:70-7. PMID: 19166091

**An online audio computer-assisted self-interview for pre-screening prior to rapid HIV testing in a vulnerable population.** Cohall AT, Senathirajah Y, Dini S, Nye A, Powell D, Powell B.  
AMIA Annu Symp Proc. 2007 Oct 11:915. PMID: 18694015

**Clustering to create user profiles of clinical and translational researchers.** Bakken S., Senathirajah Y, Johnson, SB. Poster, AMIA Annu Symp Proc. 2009.

**Design features of graphs in health risk communication: a systematic review.** Ancker JS, Senathirajah Y, Kukafka R, Starren JB. J Am Med Inform Assoc. 2006 Nov-Dec;13(6):608-18. Epub 2006 Aug 23. Review.PMID: 16929039

#### **D. Ongoing research support**

Local PI, SUNY Health Network of Excellence grant to examine feasibility of combining electronic health record data from five SUNY campuses to create a research resource.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Stewart, Mark

POSITION TITLE: Professor of Physiology & Pharmacology, and Neurology; Dean, School of Graduate Studies; Vice Dean for Research

eRA COMMONS USER NAME (credential, e.g., agency login): mstewart

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Pace University, Pleasantville, NY	BS	1983	Chemistry, Biology
SUNY Downstate Medical Center, Brooklyn, NY	PhD	1989	Neuroscience
SUNY Downstate Medical Center, Brooklyn, NY	MD	1991	Medicine
SUNY Downstate Medical Center, Brooklyn, NY	postdoc	1991-93	Neuroscience

**A. Personal Statement**

As Dean of the School of Graduate Studies and Vice Dean (equivalent to Vice President) for Research, I have experience with a number of oversight mechanisms for grants and campus research activities. I also have considerable experience training students at multiple levels from high school through advanced postdoctoral fellows and medical residents. I have trained 12 postdoctoral fellows (2 minority), 8 doctoral students (1 minority), 2 visiting scientists, 10 rotating predoctoral students (3 minority), 1 masters student (minority), 8 undergraduates (5 minority), and 5 high school students (1 minority). My access to the campus' research community and the full resources of the School of Graduate Studies also will benefit the faculty and trainees with regard to collaborative research discussions and research/education enrichment activities such as seminars and courses.

In addition, I serve as the Research Core Director for the Brooklyn Health Disparities Center, a joint venture of SUNY Downstate, the Arthur Ashe Institute for Urban Health and the Brooklyn Borough President's Office aimed at reducing health disparities among minorities and new immigrants to Brooklyn. Research projects currently focus on HIV and obstructive sleep apnea. The proposed project aligns with the goals of the Center and will expand the research core to address GI cancer-specific health disparities.

**B. Positions and Honors****Positions and Employment (current positions in italics)**

1993 – 2001 Assistant Professor (tenure-track) -- Dept Physiology & Pharmacology, College of Medicine, SUNY Downstate Medical Center, Brooklyn.

2001 – 2008 Associate Professor (tenured) -- Dept Physiology & Pharmacology, College of Medicine, Program in Neural and Behavioral Science, SUNY Downstate Medical Center, Brooklyn.

2001 – 2007 Director -- Program in Neural & Behavioral Science, School of Graduate Studies, SUNY Downstate Medical Center, Brooklyn. (Elected term: 2001-2004, 2004-2007.)

2006 – 2008 Associate Professor (tenured) -- Dept Neurology, College of Medicine, SUNY Downstate Medical Center, Brooklyn.

2008 – present Professor (tenured) -- Dept Physiology & Pharmacology, College of Medicine, SUNY Downstate Medical Center, Brooklyn.

- 2008 – present Professor (tenured) -- Dept Neurology, College of Medicine, SUNY Downstate Medical Center, Brooklyn.
- 2008 – 2009 Interim Dean – School of Graduate Studies, SUNY Downstate Medical Center, Brooklyn.
- 2008 – 2009 Vice Dean for Basic Research -- College of Medicine, SUNY Downstate Medical Center, Brooklyn.
- 2009 – present Dean – School of Graduate Studies, SUNY Downstate Medical Center, Brooklyn.
- 2009 – present Vice Dean for Research -- College of Medicine, SUNY Downstate Medical Center, Brooklyn.
- 2010 – present Program Co-Director – Program in Developmental Neuroscience, a joint program of SUNY Downstate Medical Center, Brooklyn and the Institute for Basic Research in Developmental Disabilities, Staten Island, NY.
- 2010 – present Program Co-Director – Program in Nanomedicine, a joint program of SUNY Downstate Medical Center, Brooklyn and the College of Nanoscale Science and Engineering, University at Albany (SUNY), Albany, NY.
- 2011, 2009 Visiting Scientist — Department of the Autonomic Nervous System, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan.
- 2013 ING / CUNY Medgar Evers College Pinnacle Healthcare Award
- 2015 Alpha Omega Alpha Alumni Membership, Downstate Eta Chapter of New York.
- 2015 Japan Society for the Promotion of Science Fellowship for Research in Japan. Host: Dr. Harumi Hotta, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology.

### **Other Experience and Professional Memberships**

- Member, ZNS1 SRB-W (02), National Institute of Neurological Disorders and Stroke Special Emphasis Panel, Alan Willard, Administrator. 3/19/2001.
- Ad Hoc Member, NSD-C, National Institute of Neurological Disorders and Stroke, Alan Willard, Administrator. 10/18-10/19/2001.
- Ad Hoc Member, ICP-1, Fogarty International Center, National Institutes of Health, Sandy Warren, Administrator. 07/14-07/15/2005, 10/20/2005.
- Ad Hoc Member, ICP-1 and ZRG1 BDA-G (50), Fogarty International Center, National Institutes of Health, Zakir Bengali, Administrator. 02/09 - 02/10/2006.
- Ad Hoc Member, ICP-1, Fogarty International Center, National Institutes of Health, Manana Sukhareva, Administrator. 10/20/2006, 02/22 - 02/23/2007, 07/12/2007, 06/25/2009.
- Ad Hoc Member, ZNS1-SRB-B (32), National Institute of Neurological Disorders and Stroke, Epilepsy EUREKA Program, William Benzing, Administrator. 12/06 – 12/07/2011.

Other grants review:

- The Wellcome Trust, London, United Kingdom
- Neurological Foundation of New Zealand, Auckland, New Zealand
- Epilepsy Research UK, London, United Kingdom

*Society For Neuroscience (1985 — present)*

*American Physiological Society (1986 — present)*

*International Society for Autonomic Neuroscience (2007 — present; representative-at-large 2011 — present)*

### **C. Contributions to science.**

***MECHANISMS OF SUDDEN DEATH IN EPILEPSY. Our urethane/kainite model for continuous and discrete seizures has offered unprecedented combinations of invasive and non-invasive recordings leading to a clear pathophysiological picture of the mechanisms for sudden death in epilepsy.***

1. Sakamoto, K., Saito, T., Orman, R., Koizumi, K., Lazar, J., Saliccioli, L., and **Stewart, M.** Autonomic consequences of kainic acid-induced limbic cortical seizures in rats: peripheral autonomic nerve activity, acute cardiovascular changes, and death. *Epilepsia* 49: 982-996, 2008. PMID: 18325014
2. Hotta, H., Lazar, J., Orman, R., Koizumi, K., Shiba, K., Kamran, H., and **Stewart, M.** Vagus nerve stimulation-induced bradyarrhythmias in rats. *Autonomic Neuroscience: Basic and Clinical* 151: 98-105, 2009. PMID: 19651541

3. Hotta, H., Watanabe, N., Orman, R., and **Stewart, M.** Efferent and afferent vagal actions on cortical blood flow and kainic acid-induced seizure activity in urethane anesthetized rats. *Autonomic Neuroscience: Basic and Clinical* 156: 144-148, 2010. PMID: 20510656
4. Naggar, I., Uchida, S., Kamran, H., Lazar, J., **Stewart, M.** Autonomic boundary conditions for ventricular fibrillation and their implications for a novel defibrillation technique. *Journal of Physiological Sciences* 62: 479-492, 2012. PMID: 22893479

***CARDIAC AND IMMUNE SYSTEM CONSEQUENCES OF SEIZURES. We have defined cardiovascular consequences of seizures in detail, leading to translational studies. We have also identified immune system activation from single seizures.***

1. Neufeld, G., Lazar, J. M., Chari, G., Kamran, H., Akajagbor, E., Saliccioli, L., Kassotis, J., and **Stewart, M.** Cardiac repolarization indices in epilepsy patients. *Cardiology* 114:255-260, 2009. PMID: 19672064
2. Hotta, H., Koizumi, K., and **Stewart, M.** Cardiac sympathetic nerve activity during kainic acid-induced limbic cortical seizures in rats. *Epilepsia* 50: 923-927, 2009. PMID: 19055488
3. Silverberg, J., Ginsburg, D., Orman, R., Amassian, V. E., Durkin, H., and **Stewart, M.** Lymphocyte infiltration of neocortex and hippocampus after a single brief seizure in mice. *Brain, Behavior, and Immunity* 24: 263-272, 2010. PMID: 19822204
4. Naggar, I., Lazar, J., Kamran, H., Orman, R., and **Stewart, M.** Relation of autonomic and cardiac abnormalities to ventricular fibrillation in a rat model of epilepsy. *Epilepsy Research* 108: 44-56, 2014. PMID: 24286892.

***CELLS AND CIRCUITS OF THE HIPPOCAMPUS AND SUBICULUM. We were the first to characterize bursting and regular spiking cells in the subiculum and defined cellular and projection properties of these neurons and interactions with hippocampal and parahippocampal regions.***

1. **Stewart, M.** and Wong, R. K. S. Intrinsic properties and evoked responses of guinea-pig subicular neurons in vitro. *Journal of Neurophysiology* 70: 232-245, 1993. PMID: 839557727. Harris, E., Witter, M. P., Weinstein, G. and Stewart, M. Intrinsic connectivity of the rat subiculum. I. Dendritic morphology and patterns of axonal arborization by pyramidal neurons. *Journal of Comparative Neurology* 436: 490-505, 2001. PMID: 11406828
2. Harris, E. and **Stewart, M.** Intrinsic connectivity of the rat subiculum. II. Properties of synchronous spontaneous activity and a demonstration of multiple generator regions. *Journal of Comparative Neurology* 436: 506-518, 2001. PMID: 11406829
3. Orman, R., von Gyzicki, H., Lytton, W. W., and **Stewart, M.** Local axon collaterals of area CA1 support spread of epileptiform discharges within CA1, but propagation is unidirectional. *Hippocampus* 18: 1021-1033, 2008. PMID: 18548581
4. Kunitake, A., Kunitake, T. and **Stewart, M.** Differential modulation by carbachol of four separate excitatory afferent systems to the rat subiculum in vitro. *Hippocampus* 14: 986-999, 2004. PMID: 15390173

***CELLS AND CIRCUITS OF PARAHIPPOCAMPAL CORTICES. We characterized parahippocampal cells and circuits, including presubiculum, parasubiculum, and entorhinal cortex.***

1. Funahashi, M. and Stewart, M. Presubicular and parasubicular cortical neurons of the rat: electrophysiological and morphological properties. *Hippocampus* 7: 117-129, 1997. PMID: 9136044
2. Funahashi, M. and Stewart, M. Presubicular and parasubicular cortical neurons of the rat: functional separation of deep and superficial neurons in vitro. *Journal of Physiology (London)* 501: 387-403, 1997. PMID: 9192310
3. Funahashi, M. and Stewart, M. Properties of gamma-frequency oscillations initiated by propagating population bursts in retrohippocampal regions of rat brain slices. *Journal of Physiology (London)* 510: 191-208, 1998. PMID: 9625877
4. Funahashi, M., Harris, E. and **Stewart, M.** Re-entrant activity in a presubiculum — subiculum circuit generates epileptiform activity in vitro. *Brain Research* 849: 139-146, 1999. PMID: 10592295

***SYNCHRONOUS HIPPOCAMPAL ACTIVITY (THETA RHYTHM). We defined the projections from medial septal nucleus to hippocampal areas that are responsible for hippocampal theta rhythm.***

1. Stewart, M. and Fox, S. E. Two populations of rhythmically bursting neurons in the rat medial septum are revealed by atropine. *Journal of Neurophysiology* 61: 982-993, 1989. PMID: 2723736



U24-MD006960 Taylor (Contact PI) 9/1/2012 to 6/30/2016  
"Urban Universities for HEALTH – The Power of SUNY"  
National Institute on Minority Health Disparities through the Association of American Medical Colleges  
Overall goal: Identify and improve strategies for addressing training of underrepresented minority students in healthcare.  
Role: Executive Council Member

1R25-NS079211-01 Levine, Rosenbaum (co-PIs) 4/1/2012 to 3/31/2017  
"SUNY Downstate 'R Train:' Neurology Research Education Program."  
National Institute of Neurological Disorders and Stroke  
Overall goal: Neurology research for residents and fellows  
Role: Chair of Oversight and Training Committee, Mentor in epilepsy focus

**Completed Research Support (ending within the last 3 years)**

Percy Mem. Research Award Kollmar, Stewart, Silverman, Sundaram (co-PIs) 7/1/2013 to 12/31/2014  
"Restoration of recurrent-laryngeal-nerve function after injury in a rat model."  
American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF).  
Overall goal: Study reinnervation of vocal folds after damage to recurrent laryngeal nerve.  
Role: Co-PI

D18HP23014 Hill (PI) 9/1/2011 to 8/31/2014.  
"Pipeline Access to Health-careers (PATH)."  
Health and Human Resources Administration (HRSA)/ Health Careers Opportunity Program (HCOP)  
Overall goal: Develop a pipeline for under-represented minority students in graduate health education.  
Role: Contributor (assist with recruitment and selection for the Graduate Studies component of Early Medical Education Program).

## BIOGRAPHICAL SKETCH

NAME	POSITION TITLE		
Patricia Thompson, Ph.D.	Full Professor		
eRA COMMONS USER NAME			
pthompson			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Angelo State University, San Angelo, TX	B.S.	1986	Biology
Univ. of TX Health Science Ctr., San Antonio, TX	Ph.D.	1993	Immunology/Microbiology
Southwest Research Foundation, San Antonio, TX	Postdoc	1993-	Virology
Univ. of TX Health Science Ctr, San Antonio, TX	Postdoc	1994-	Molecular Immunology
National Ctr. for Toxicology Res. , Jefferson, AK	Postdoc	1996-	Molecular Epidemiology

### A. Personal Statement

I am a laboratory-trained molecular and cellular biologist with interest in breast and colorectal cancer molecular biology and epidemiology. My research focus is in translating knowledge of breast and colorectal cancer biology to prevention of primary disease and metastasis in early stage patients. Over the past several years, I have focused my research efforts in the area of prevention with a special interest in applying strategies to study the impact of genetic susceptibility and tumor characteristics to prevention in high risk individuals. For breast cancer, this has included understanding the role of differences across populations by socioeconomic status, race/ethnicity, and population migration that may explain heterogeneity in the pattern of breast tumor subtypes across different populations and their relationship to patient outcomes. For colorectal cancer, my research focuses on identification of high risk preneoplastic lesions to better inform on the cost benefits of chemoprevention with non-steroidal anti-inflammatory agents, colonoscopy and age of initiation of screening and surveillance intervals.

I recently joined the faculty at Stony Brook University in the Department of Pathology as a Professor and as the Associate Director of Basic Science for the Stony Brook Cancer Center. I have extensive experience successfully mentoring young investigators (undergraduate, pre and post-doctoral and early career faculty). I am a participating mentor in the PRIDE (Programs to Increase Diversity among Individuals Engaged in Health- Related Research) and also a member of the GMaP program (Geographical Management of Cancer Health Disparities) through the Center to Reduce Cancer Health Disparities (CRCHD) at the NCI. Since 2007, I have served as one of the U.S. PIs for the ELLA Binational Breast Cancer Study, including playing a major role in its inception, design and implementation. I was a co-PI on a previous Susan G. Komen for the Cure Predoctoral Training Fellowship in Breast Cancer Health Disparities that resulted in five publications and very successful placement of our pre-doctoral students into research in diverse areas to support breast cancer research, treatment and community practice among underserved populations. This includes one trainee in medical school, another as an epidemiologist for the penal system for women's health, and another who received a full scholarship at UC Berkley to pursue her PhD in women's and children's cancers. In addition, I served as the Co- Director of the Career Development Program of the AZ SPORE Grant in GI cancers for seven years, which I continued after taking on the PI role of the GI SPORE. For GI cancers, my training experience has largely been focused on translation research and MD or MD/PhD fellows.

Personally, I am from an underserved/unrepresented community in West Texas where I attended the local College on an ROTC academic scholarship. As the first college graduate in my family, I was introduced to the possibility of research science as a profession from recruiters that came to my local college. With strong career mentorship, I was able to progress in what often felt like a foreign culture. As a result of my background and ties to my home town and family, I know the disparity that exists between cancer care in the underserved community and cancer care at the top academic cancer centers in the U.S. I also truly appreciate the array of challenges that students and early career investigators face when they come from underserved backgrounds and the need for a high bar and sustained motivation often based on wanting to make a difference. I am, thus highly committed to

diversity in research sciences as I believe that education and empowerment of a few impact on the whole leading to advancement for all people.

## B. Position and Honors

### Professional Experience

03/96-06/99	Molecular Biologist and Staff Scientist, Div. of Molecular Epidemiology, National Ctr. for Toxicological Research, Jefferson, Arkansas
07/99-08/01	Research Assistant Professor, Dept. of Epidemiology, University of Texas MD Anderson Cancer Center, Houston, Texas
08/01-10/07	Assistant Professor, Department of Pathology, University of Arizona Cancer Center, Tucson, Arizona
12/03-Present	Adjunct Professor, Department of Nutritional Sciences, University of Arizona, Tucson, Arizona
10/07-01/08	Research Assistant Professor, Department of Pathology, University of Arizona, Tucson, Arizona
01/08-08/10	Assistant Professor, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona
09/10-10/14	Associate Professor, Cellular and Molecular Medicine, University of Arizona, Tucson Arizona
11/11-10/14	Program Leader for the Cancer Prevention and Control Program, University of Arizona Cancer Center
10/14-present	Professor of Pathology, Stony Brook University, Stony Brook NY
10/14-present	Associate Director for Basic Research, Stony Brook Cancer Center, Stony Brook, NY

## C. Selected Publications: 15 of 104 peer reviewed publications of relevance to the application

Of 120 peer reviewed publications, I have selected 15 most recent publications for which I served as the primary mentor of the first author. I have indicated with an "\*" which are clinical and a "†" for those that Dr. Stoepck and I have co-mentored mentee)

1. \*Brewster AM, Do KA, **Thompson PA**, Hahn KM, Sahin AA, Cao Y, Stewart MM, Murray JL, Hortobagyi GN, Bondy ML. Relationship between epidemiologic risk factors and breast cancer recurrence. *Journal of Clinical Oncology*. 2007;25(28):4438–44.
2. \*Bartley AN, **Thompson PA**, Buckmeier JA, Kepler CY, Hsu CH, Snyder MS, Lance P, Bhattacharyya A, Hamilton SR. Expression of gastric pyloric mucin, MUC6, in colorectal serrated polyps. *Modern Pathology*. 2010;23(2):169–76.
3. Egan JB, **Thompson PA**, Ashbeck EL, Conti DV, Duggan D, Hibler E, Jurutka PW, Leroy EC, Martínez ME, Mount D, Jacobs ET. Genetic polymorphisms in vitamin D receptor VDR/RXRA influence likelihood of colon adenoma recurrence. *Cancer Research*. 2010;70(4):1496–504.
4. Egan JB, **Thompson PA**, Vitanov MV, Bartik L, Jacobs ET, Haussler MR, Gerner EW, Jurutka PW. Vitamin D receptor ligands, adenomatous polyposis coli, and the vitamin D receptor FokI polymorphism collectively modulate  $\beta$ -catenin activity in colon cancer cells. *Molecular Carcinogenesis*. 2010;49(4):337–52.
5. Flowers M, Schroeder JA, Borowsky AD, Besselsen DG, Thomson CA, Pandey R, **Thompson PA**. Pilot study on the effects of dietary conjugated linoleic acid on tumorigenesis and gene expression in PyMT transgenic mice. *Carcinogenesis*. 2010;31(9):1642–9.
6. \*Brewster AM, **Thompson, PA**, Sahin AA, Do K, Edgerton M. Murray JL, Tsavachidis S, Zhou R, Liu Y, Zhang L Mills G, Bondy M. Copy number imbalances between screen and symptom-detected breast cancers and impact on disease-free survival. *Cancer Prevention Research*. 2011;4(10):1609–16.
7. Vargas AJ, Wertheim BC, Gerner EW, Thomson CA, Rock CL, **Thompson PA**. Dietary polyamine intake and risk of colorectal adenomatous polyps, 2012 *AJCN* Jul;96(1):133-41.
8. Wertheim BC, Smith JW, Fang C, Alberts DS, Lance P, **Thompson PA**. Risk modification of colorectal adenoma by CYP7A1 polymorphisms and the role of bile acid metabolism in carcinogenesis. *Cancer Prev Res (Phila)*. 2012 Feb;5(2):197-204.
9. †Butalla AC, Crane TE, Patil B, Wertheim BC, **Thompson P**, Thomson CA. Effects of a carrot juice intervention on plasma carotenoids, oxidative stress, and inflammation in overweight breast cancer survivors. *Nutr Cancer*. 2012;64(2):331-41.

10. Cruz GI, Martínez ME, Natarajan L, Wertheim BC, Gago-Dominguez M, Bondy M, Daneri-Navarro A, Meza-Montenegro MM, Gutierrez-Millan LE, Brewster A, Schedin P, Komenaka IK, Castelao JE, Carracedo A, Redondo CM, **Thompson PA**. Hypothesized role of pregnancy hormones on HER2+ breast tumor development. *Breast Cancer Res Treat*. 2013 Jan;137(1):237-46.
11. \*Algotar AM, Stratton MS, Ahmann FR, Ranger-Moore J, Nagle RB, **Thompson PA**, Slate E, Hsu CH, Dalkin BL, Sindhwani P, Holmes MA, Tuckey JA, Graham DL, Parnes HL, Clark LC, Stratton SP. Phase 3 clinical trial investigating the effect of selenium supplementation in men at high-risk for prostate cancer. *Prostate*. 2013 Feb 15;73(3):328-35..
12. \*Bartley AN, Parikh N, Hsu CH, Roe DJ, Buckmeier JA, Corley L, Phipps RA, Gallick G, Lance P, **Thompson PA\***, Hamilton SR. Colorectal adenoma stem-like cell populations: associations with adenoma characteristics and metachronous colorectal neoplasia. *Cancer Prev Res* 2013. 6(11):1162-70. *\*co-senior author with Hamilton*
13. †Miller JA, Lang JE, Ley M, Nagle R, Hsu CH, **Thompson PA**, Cordova C, Waer A, Chow HH. Human breast tissue disposition and bioactivity of limonene in women with early-stage breast cancer. *Cancer Prev Res (Phila)*. 2013 6(6):577-84. PMID: 3692564.
14. Liu Y, Zhou R, Baumbusch LO, Tsavachidis S, Brewster AM, Do KA, Sahin A, Hortobagyi GN, Taube JH, Mani SA, Aaroe J, Warnberg F, Borresen-Dale AL, Mills GB, **Thompson PA**, Bondy ML Genomic copy number imbalances associated with bone and non-bone metastasis of early-stage breast cancer. *Breast Cancer Res Treat*. 2014 Jan;143(1):189-201 *Thompson and Bondy co-senior authors*
15. \*L. Tsikitis, DW. Larson, M Huebner, CM. Lohse, **PA. Thompson**. Predictors of Recurrence Free Survival for Patients with Stage II and III Colon Cancer. *BMC Cancer*. 2014 May 16;14:336

## D. Research Support

### Current

1R01 CA151708-01A1 (Thompson-Carino/Lance, Joint PIs) 08/01/11 – 06/30/15 (in no cost extension)

NIH/NCI

Role: Co-I

Selenium Colorectal Cancer Chemoprevention Trials

The major goals of this program are to follow remaining Se treatment in participants through study completion for all 1,800 participants in 2013, and for data analysis and reporting. Another aim addresses the risk for T2D incurred by the one third of Americans using Se-containing multivitamin and multi-mineral supplements

1U01CA153086 (Futscher, PI) 07/01/10-06/30/15

NIH/NCI

Epigenetic Features of Pregnancy-Associated Breast Cancer in Hispanic Women

Role: Co-Investigator

The immediate objective of this research project is to compare the epidemiological and epigenetic profiles of breast cancer tumors diagnosed in the transient postpartum period of increased risk against those that are diagnosed outside this period.

1R01 CA49417-01A1 (Thomson, PI) 09/20/10-07/31/15

NIH/NCI

Evaluation of Di-indolylmethane supplementation to modulate tamoxifen efficacy in premenopausal breast cancer patients

Role: Co-Investigator

The major goal of this research is to test the efficacy and safety of diindolylmethane in women taking tamoxifen as adjuvant therapy for breast cancer

N01-WH-2-2115 (Prentice, PI) 10/01/12-09/31/15

NIH/NHLB

Women's Health Initiative (WHI) Extension Study Vanguard Clinical Center

Role: Co-Investigator

Extension Study of Health Outcomes in WHI Study Population

1R01 CA1615301A1 (Thompson-Carino /Stopeck, Joint PIs)

07/01/11-04/30/16

NIH/NCI

NSAID effects on clinical and imaging breast biomarkers

Role: Co-I

The goal of this project is to investigate the effect of sulindac combined with aromatase inhibitor on breast density measured by MRI

R01CA157595 (Ignatenko, PI) 07/01/12-04/30/17

NIH/NCI

Role of Kallikrein 6 expression and secretion in colon cancer

Role: Co-Investigator

The goal of the project is to investigate the role of kallikrein 6 secretion as a biomarker of colorectal cancer metastasis. My role is to provide technical expertise for the conduct of the biomarker analyses in blood and tissue.

1R01CA172511-01 (Thompson-Carino/Bondy/Brewster, MPIs) 01/01/13-12/31/17

NIH/NCI

Risk Prediction for ER Negative Breast Cancer Recurrence

Role: Co-I

The goal of this study is to validate a risk prediction model for early stage ER negative breast cancer based on tumor genotype and to assess its performance in African American, Hispanic and Non-Hispanic Whites.

### **Completed Work**

P30 CA023074-31 (Alberts, PI) 07/1/04 – 06/30/14

NIH/NCI

Arizona Cancer Center Support Grant

Role: Program Leader, Cancer Prevention and Control

The major goal of this project is to provide organizational infrastructure for the promotion of interdisciplinary research and the collective use of resources. Funds for Dr. Lance support his role as Program Leader and his role as Senior Leader as Chief Cancer Control Officer at the Arizona Cancer Center.

P50CA95060 (Thompson-Carino, PI) 04/01/12 - 03/31/14

NIH/NCI

Specialized Program of Research Excellence in GI Cancer

Role: PI, Co-Leader, Project 1

The goal of this interdisciplinary Specialized Program of Research Excellence in GI cancer is to prevent and cure GI cancers, through studies in prevention, genetics and therapeutics.

1R01ES019879 (Thomas, PI) 08/06/10-03/31/14

NIH/NIEHS

Methods for pathway modeling with application to folate

Role: Site PI

The overall goal of the project is to develop novel modeling techniques to study in silico the impact of genetic variation on complex biochemical pathways. The model system is folate metabolism and my role is to provide expertise and data from the two colon cancer prevention studies to build and validate the new tools.

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Shivakumar Vignesh, MD		POSITION TITLE Associate Professor, Department of Medicine, Chief, Division of Gastroenterology and Hepatology Director, Gastroenterology Fellowship Program	
eRA COMMONS USER NAME SVIGNESH			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Madras Medical College, Madras, India	MD	1990-1995	Medicine
Robert Wood Johnson University Hospital, NJ		1997-2000	Internal Medicine- Internship/Residency
Albert Einstein Medical Center, Philadelphia, PA		2000-2002	Gastroenterology Fellowship
Yale New Haven Hospital, Yale Univ. School of Medicine, New Haven, CT		2002-2003	Gastroenterology Fellowship
Medical University of South Carolina, Charleston, SC		2006-2007	Advanced Endoscopy

### A. Personal Statement

I am a Gastroenterologist with an interest in advanced endoscopic imaging, gastrointestinal cancer research and medical education. I have a strong interest in diagnosis and treatment of pancreatic cancer using endoscopic ultrasound guided techniques. I have the expertise and motivation necessary to successfully collaborate with other clinicians, educators and basic scientists to carry out the proposed research.

My background in gastroenterology, with specific training and expertise in advanced endoscopy is well suited to the pilot project on pancreatic cancer that is a component of the P20 grant. The use of fine-needle biopsies to create pancreatic organoids is novel and will be significant for those patients that are not surgical candidates. As an advanced endoscopy fellow at Medical University of South Carolina, I initiated and conducted a pilot study on contrast enhanced endoscopic ultrasound to diagnose malignant pancreatic and liver lesions. Working at a major cancer center and having participated in many GI oncology clinical trials with sample acquisition and storage in tissue banks has given me valuable experience that would be useful with our proposed study.

I successfully collaborated with both clinical and basic scientists on many funded trials over the last 10 years in my academic career. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. In summary, I have a demonstrated record of successful collaborative research and my expertise and experience are valuable to the completion of the proposed project.

### B. Positions and Honors

2003-2006 Director of the Gastroenterology Clinic, VACT Healthcare system  
2004-2006 Chair, Surgical and invasive procedures committee, VACT Healthcare System  
2014-Present Chief, Division of Gastroenterology and Hepatology

### Hospital Appointments:

2003- 2006 Attending Physician, Internal Medicine, Section of Digestive Diseases, Yale  
New-Haven Hospital. New Haven, CT-06520  
2003-2006 Attending Physician, Internal Medicine, Section of Digestive diseases, VACT  
Healthcare System, West Haven, CT- 06516  
2006-2007 Attending Physician, Gastroenterology and Hepatology, Medical University of  
South Carolina, Charleston, SC – 29425  
2007- 2008 Attending Physician, Gastroenterology and Hepatology, M.S. Hershey Medical

Center, Penn State University, Hershey, PA 17033  
 2008-2014 Attending Physician, Gastrointestinal Oncology, Moffitt Cancer Center, 12902  
 Magnolia Drive, Tampa, FL

# **Academic Appointments:**

2003-04 Clinical Instructor in Medicine, Section of Digestive Diseases, Yale University School of  
 Medicine  
 2004-07 Assistant Professor of Medicine, Section of Digestive Diseases, Yale University  
 2006-07 Faculty, Division of Gastroenterology, Medical University of South Carolina, Charleston, SC  
 2007-08 Director of Endoscopic Ultrasound / Therapeutic Endoscopy, Assistant  
 Professor of Medicine, Division of Gastroenterology and Hepatology, M.S. Hershey Medical  
 Center, Hershey, PA  
 2008-2014 Associate Member, Department of GI Oncology, Moffitt Cancer Center  
 2008-2014 Associate Professor, Department of Oncologic Sciences, University of South Florida  
 2014-Present Associate Professor, Department of Medicine, SUNY Downstate Medical Center

## **B. Selected Peer-reviewed Publications or manuscripts in press**

1. Morse B, Centeno V, **Vignesh S**; Autoimmune Pancreatitis: Updated concepts of a challenging  
 diagnosis. AM J Med. 2014 May 14.
2. Brand RE, Adai AT, Centeno BA, Lee LS, Rateb G, **Vignesh S**, et al. A MicroRNA-based Test  
 Improves Endoscopic Ultrasound-Guided Cytologic Diagnosis of Pancreatic Cancer Clinical  
 Gastroenterology and Hepatology: 2014 Oct;12(10):1717-23.
3. Harris CL, Toloza EM, Klapman JB, **Vignesh S**, Rodriguez K, Kaszuba FJ. Minimally invasive  
 mediastinal staging of non-small cell lung cancer: emphasis on ultrasonography-guided fine-needle  
 aspiration. Cancer Control. 2014 Jan;21(1):15-20.
4. Fernandez DC, Hoffe SE, Barthel JS, **Vignesh S**, Klapman JB, Harris C, Almhanna K, Biagioli MC,  
 Meredith KL, Feygelman V, Rao NG, Shridhar R. Stability of endoscopic ultrasound-guided fiducial  
 marker placement for esophageal cancer target delineation and image-guided radiation therapy.  
 Pract Radiat Oncol. 2013 Jan-Mar;3(1):32-9. doi: 10.1016/j.prro.2012.02.006. Epub 2012 Mar 30.
5. Wong J, Weber J, Centeno BA, **Vignesh S**, Harris CL, Klapman JB, Hodul P. High-grade dysplasia  
 and adenocarcinoma are frequent in side-branch intraductal papillary mucinous neoplasm measuring  
 less than 3 cm on endoscopic ultrasound. J Gastrointest Surg. 2013 Jan;17(1):78-84; discussion  
 p.84-5.
6. **Vignesh S**, Hoffe SE, Meredith KL, Shridhar R, Almhanna K, Gupta AK. Endoscopic therapy of  
 neoplasia related to Barrett's esophagus and endoscopic palliation of esophageal cancer. Cancer  
 Control. 2013 Apr;20(2):117-29. Review.
7. Pimiento JM, Weber J, Hoffe SE, Shridhar R, Almhanna K, **Vignesh S**, Karl RC, Meredith KL.  
 Outcomes associated with surgery for T4 esophageal cancer. Ann Surg Oncol. 2013  
 Aug;20(8):2706-12.
8. Romagnuolo J, Hoffman B, Vela S, Hawes R, **Vignesh S**. Accuracy of contrast-enhanced harmonic  
 EUS with a second generation perflutren lipid microsphere contrast agent (with Video). Gastrointest  
 Endosc. 2011 Jan;73(1):52-63.
9. **Vignesh S**, Hoffe SE, Wasif Saif M. EUS-Guided Pancreatic Diagnosis and Beyond. Journal of the  
 Pancreas. 2011 Mar 9;12(2):86-91.

## **C. Research Support**

None

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Jennie L. Williams		POSITION TITLE Associate Professor of Preventive Medicine	
eRA COMMONS USER NAME (credential, e.g., agency login) jenniewilliams			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY

**A. Personal Statement:**

My present research evaluates colorectal cancer racial health disparities. As part of my studies, I am defining the effect and mode of action of novel NSAID derivatives that have distinct pharmacological advantages (safety and superior efficacy) compared to conventional NSAIDs. We are assessing mechanisms of action with particular emphasis on their effect on miRNAs; which represent emerging major regulators of gene expression especially as it relates to cancer. miRNAs are also of interest to us due to our hypothesis that their differential expression and dysregulation are in part accountable for racial health disparity. As such, we are comparing in a systematic way genetic and epigenetic factors related to cancer racial health disparities between African, Hispanic and Caucasian Americans in regard to cancer incidence and death. In general, all mechanistic differences as it relates to ethnicity are being evaluated. IRB approvals are in place. My RO1 has served to drive, to a large degree, the SUNY Stony Brook GI BioBank's collection process of colorectal tumor and adjacent normal tissue, the collection of longitudinal clinical data, blood and stool, over the past 5 years. I am pleased that this tissue, fluid and data collection has benefited multiple other investigators at SUNY Stony Brook launching other related translational projects. This BioBank has banked over 500 patients including > 100 patients with colorectal cancer. Over the past year, we have reached out to initiate the development of a parallel SUNY Downstate GI BioBank for which we are requesting support in this P20 application. In addition to research, I am co-PI of two NIH/NIGMS education grants. Also of importance to this proposal is the minority access to research careers (MARC). The ultimate objective of this program is to provide assistance and guidance to underrepresented Stony Brook University students who have an aptitude for science but lack the skills needed for transition to research at the PhD level. We provide career information and send students to conferences and workshops. These venues allow them to learn skills such as grantsmanship, networking and data presentation (Poster and oral presentation). We encourage basic and translational research at summer intramural and extramural programs. I look forward to continuing to mentor many of the students by chairing the steering committee that will oversee the development of a Scholars in Biomedical Sciences in Cancer Health Disparities and anticipate that I will serve as a research mentor for URM and non-URM graduate students who seek to gain more experience in translational research. I also look forward to the opportunity to educate established cancer research investigators more on Cancer Health Disparities.

**B. Positions and Honors**Positions

1992-1995	Research Fellow, Massachusetts General Hospital and Harvard Medical School, Boston, MA
1995-1999	Research Fellow, New England Regional Primate Research Center, Harvard Medical School, Southborough, MA

1999-2000	Research Associate, Cytoc Corporation, Boxborough, MA
2000- 2004	Research Fellow, New York Medical College and Institute for Cancer Prevention, Valhalla, NY
2004-2014	Research Assistant Professor of Medicine, SUNY Stony Brook, Stony Brook, New York
2011-	Instructor and course developer ("Laboratory Techniques in Cancer Biology "Bio 364), SUNY Stony Brook, Stony Brook, New York
2014-	Associate Professor of Preventive Medicine with tenure, SUNY Stony Brook, New York

### Honors

1986-1988 Proctor and Gamble Fellowship (Purdue University)  
 1988-1991 Black and Ethnic Fellowship (Purdue University)  
 1992-1995 NIH Minority supplement grant (Massachusetts General Hospital)  
 1995-1997 NIH Minority supplement grant (Harvard Medical School)  
 2004-2004 NIH Minority supplement grant (Stony Brook University)  
 2008 Minority Access Ninth National Role Model Award

### Committees and Positions (selected)

2006 HHMI	Academic Year Scholars Selection Committee
2006-2012	Co-Director Long Island Group Advancing Science Education (LIGASE) Bio-Prep Summer program
2007-2011	LIGASE Mentor: High School Protein Modeling Project
2007	Reviewer (TRO Breast Cancer Applications)
2007	Organizing Committee: Cancer Chemoprevention Symposium (Crete, Greece)
2008	Peer Reviewer (Carcinogenesis)
2008-2012	Annual Biomedical Research Conference for Minority Students (Poster-Judge)
2009	NIH Grant Review Committee Challenge Grants Panel 10
2010-2011	NIH Grant Review Adhoc Committee
2011	Journal Peer Reviewer (International Union of Biochemistry and Molecular Biology (IUBMB Life))
2011	AACR's MICR Professional Advancement Roundtable Committee
2011	Review Members of a Bio-marker Special Emphasis Panel
2011-	present NIH Grant Review Member (Full member/Cancer Biomarker Study Session)
2012	Journal Peer Reviewer (Journal of Molecular Medicine)
2012	Journal Peer Reviewer (Future Medicinal Chemistry)

### **C. Selected Peer-reviewed Publications** *Most relevant to the current application*

1. **Williams JL**, Borgo S, Hasanl, Castillo E, Traganos F, Rigas, B. Nitric Oxide-releasing nonsteroidal anti-inflammatory drugs (NSAIDS) alter the kinetics of human colon cancer cell lines more effectively than traditional NSAIDs: implications for colon cancer chemoprevention. *Cancer Research* 2001; 61: 3285-3289.
2. **Williams JL**, Nath N, Chen J, Hundley TR, Gao J, Kopelovich L, Kashfi K, Rigas B. Growth inhibition of human colon cancer cells by nitric oxide (NO)-donating aspirin is associated with cyclooxygenase-2 induction and beta-catenin/T-cell factor signaling, nuclear factor-kappaB, and NO synthase 2 inhibition: implications for chemoprevention. *Cancer Res.* 2003; 63: .7613-8.
3. **Williams JL**, Kashfi K, Ouyang N, del Soldato P, Kopelovich L, Rigas B. NO-donating aspirin inhibits intestinal carcinogenesis in Min (APC(Min/+)) mice. *Biochem Biophys Res Commun.* 2004; 313: 784-8.
4. **Williams JL**, Ouyang N, Ji P, Liu X, Rigas B. NO-donating aspirin inhibits the activation of NF-kB in human cancer cell lines and Min mice. *Carcinogenesis* 2008; 29: p.390-397 PMC2679698
5. Ouyang N, **Williams JL**, Rigas B. NO-donating aspirin inhibits angiogenesis by suppressing VEGF expression in HT-29 human colon cancer xenografts developed in an immunocompromised mouse model. *Carcinogenesis* 2008; 29:1794-8 PMC2527643
6. **Williams JL**, Rigas B. NO-donating NSAIDs and cancer: an overview with a note on whether NO is required for their action. *Nitric Oxide.* 2008;19:199-204 PMC2560981
7. **Williams JL**, Ji P, Ouyang N, Kopelovich L, Rigas B. Protein nitration and nitrosylation by NO-donating aspirin in colon cancer cells: Relevance to its mechanism of action. *Exp Cell Res.* 2011; 317: 1359-67.

8. Foreman JE, Chang WC, Palkar PS, Zhu B, Borland MG, **Williams JL**, Kramer LR, Clapper ML, GonzalezFJ, Peters JM. Functional characterization of peroxisome proliferator-activated receptor- $\beta/\delta$  expression in colon cancer. *Mol Carcin.* 2011; 50:884-900. PMC2790141
9. Gao L, **Williams JL**. Nitric oxide-donating aspirin induces G2/M phase cell cycle arrest in human cancer cells by regulating phase transition proteins. . *Int J. Oncol*, 41: 2012 325-30.
10. Ouyang N, Ji, P, **Williams JL**. A novel NSAID derivative, phospho-ibuprofen, prevents AOM-induced colon cancer in rats. . *Int J. Oncol* 2013; 42: 643-650 PMC3982714
11. Katz M, Parrish ME, Li E, Zhang Y, Zhu W, Shroyer K R, Bergamaschi R, **Williams JL**. The Effect of Race/Ethnicity on the Age of Colon Cancer Diagnosis. *Journal of Health Disparities Research and Practice* 2013 <http://digitalscholarship.unlv.edu/jhdrp/vol6/iss1/5/>
12. Xu X, Zhang Y, **Williams JL**, Antoniou E, McCombie W R, Wu S, Zhu W, Davidson NO, Denoya P, Li E. Parallel comparison of Illumina RNA-Seq and Affymetrix microarray platforms on genomic profiles generated from 5-aza-deoxy-cytidine treated HT-29 colon cancer cells and simulated datasets. *BMC Bioinformatics* 2013, 14(Suppl 9):S1. PMC3687991
13. Holder AA, Taylor P, Magnusen AR, Moffett ET, Meyer K, Hong Y, Ramsdale SE, Gordon M, Stubbs J, Seymour LA, Acharya D, Weber RT, Smith PF, Dismukes GC, Ji P, Menocal L, Bai F, **Williams JL**, Cropek DM, Jarrett WL. Synthesis, characterization, and preliminary anticancer photodynamic therapeutic in vitro studies of mixed-metal binuclear ruthenium(II)-vanadium(IV) complexes. *Dalton Trans.*, 2013, 42, 11881-11899. PMC3751419
14. Li E, Ji P, Ouyang N, Zhang Y, Wang XY, Rubin DC, Davidson NO, Bergamschi R, Shroyer KR, Birke S, Zhu W, **Williams JL**. Differential expression of miRNAs in colon cancer between African and Caucasian Americans: implications for cancer racial health disparities. *Int J. Oncol*, 2014; 45:587-594 PMC409196
15. Wang X, Yu X, Zhu W, McCombie WR, Antoniou E, Powers RS, Davidson NO, Li E, **Williams J**. A trimming-and-retrieving alignment scheme for reduced representation bisulfite sequencing. *Bioinformatics*. 2015 Feb 13. [Epub ahead of print]

#### D. Research Support

##### Current

NIGMS: BioPREP: 09/01/13-8/31/18  
 Biology Partnership in Research and Education Program. National  
 institute of general medical sciences,  
 Role: Co-PI Percent effort: 20%

##### Completed

T34GM00865511A1 6/01/09-05/31/14

Nat. Inst. of General Med. Sci.

Role: Co-PI Percent effort: 20% (no salary)

The goal of this grant is to increase the number of underrepresented minority Ph.D. scientists in biomedical research. I do not receive a salary from this grant.

R01CA140487-01A1

01/01/09-12/31/14

NIH/NCI

Role: PI Percent effort: 60%

This grant (titled Phosphosulindac, miRNAs and cancer racial disparity) evaluates colorectal cancer health disparities

**Project/Performance Site Location(s)****Project/Performance Site Primary Location**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY, Stony Brook University  
Duns Number: 8048782470000  
Street1\*: STONY BROOK UNIVERSITY  
Street2: The Office of Sponsered Programs  
City\*: STONY BROOK  
County:  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 117940000  
Project/Performance Site Congressional District\*: NY-001

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**Project/Performance Site Location 1**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY Downstate Medical Center  
DUNS Number: 0407963280000  
Street1\*: 450 Clarkson Avenue  
Street2:  
City\*: Brooklyn  
County:  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 112030000  
Project/Performance Site Congressional District\*: NY-009

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**Project/Performance Site Location 2**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Cold Spring Harbor Laboratory  
DUNS Number: 0659687860000  
Street1\*: 1 Bungtown Road  
Street2:  
City\*: Cold Spring Harbor  
County:  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES

Zip / Postal Code\*: 117242209

Project/Performance Site Congressional District\*: NY-003

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File Name

**Additional Location(s)**

## RESEARCH &amp; RELATED Other Project Information

<b>1. Are Human Subjects Involved?*</b> <input checked="" type="radio"/> Yes <input type="radio"/> No	
1.a. If YES to Human Subjects	
Is the Project Exempt from Federal regulations? <input type="radio"/> Yes <input checked="" type="radio"/> No	
If YES, check appropriate exemption number:      — 1 — 2 — 3 — 4 — 5 — 6	
If NO, is the IRB review Pending? <input checked="" type="radio"/> Yes <input type="radio"/> No	
IRB Approval Date:	
Human Subject Assurance Number	00000125
<b>2. Are Vertebrate Animals Used?*</b> <input checked="" type="radio"/> Yes <input type="radio"/> No	
2.a. If YES to Vertebrate Animals	
Is the IACUC review Pending? <input checked="" type="radio"/> Yes <input type="radio"/> No	
IACUC Approval Date:	
Animal Welfare Assurance Number	A3011-01
<b>3. Is proprietary/privileged information included in the application?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
<b>4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
4.b. If yes, please explain:	
4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? <input type="radio"/> Yes <input type="radio"/> No	
4.d. If yes, please explain:	
<b>5. Is the research performance site designated, or eligible to be designated, as a historic place?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
5.a. If yes, please explain:	
<b>6. Does this project involve activities outside the United States or partnership with international collaborators?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
6.a. If yes, identify countries:	
6.b. Optional Explanation:	
<b>7. Project Summary/Abstract*</b>	Filename P20_abstract031915.pdf
<b>8. Project Narrative*</b>	OverallProjectNarrativefinal.pdf
<b>9. Bibliography &amp; References Cited</b>	OVERALL_References_031915.pdf
<b>10. Facilities &amp; Other Resources</b>	FacRes_comb_F.pdf
<b>11. Equipment</b>	Equip_comb_F.pdf
<b>12. Other Attachments</b>	Biosketch_Binder1.pdf

## ABSTRACT

Two SUNY medical campuses (SUNY Stony Brook and SUNY Downstate) serving underrepresented minority communities with cancer health disparities are partnering with the NCI designated Cancer Center at the Cold Spring Harbor Laboratories to evaluate biological and genetic differences in GI cancers (colorectal and pancreatic) that may link to differences in cancer incidence and outcome observed in racial and ethnic minorities (URM). For the Cancer Research Program, we aim to augment the representation of underrepresented minorities in the collection of biospecimens and linked high dimensional 'omic datasets generated from these biospecimens. In this planning grant we plan to develop a SUNY Downstate GI Biobank that operates in parallel to the SUNY Stony Brook GI BioBank using standard operating procedures. We are planning the development of an integrative biomedical informatics platform that will link the biospecimens with longitudinal clinical data and with the data generated from these specimens. An initial step in the planning procedure is to develop a consensus of what data elements to include and for developing a controlled vocabulary. To increase community participatory research among racial and ethnic minority populations, we plan to leverage the resources and expertise of the SUNY Downstate Brooklyn Health Disparities Center (led by Dr. Moro Salifu) in developing community education and outreach programs in underserved communities with a high proportion of racial and ethnic minorities. The collection of biospecimens will be driven by two pilot research projects, P1 and P2. In P1, we propose to compare genomic and epigenetic profiling of URM colon cancers with non URM colon cancers. In P2, we propose to test the feasibility of adapting an innovative 3-D method to grow pancreatic organoids (miniature pancreas) from progenitor cells (developed in Dr. Tuveson's laboratory at CSHL) from fine needle core biopsies of human pancreatic cancers collected at the two SUNY medical campuses. We plan to compare genomic and epigenomic profiling of URM pancreatic organoids with those of non-URM organoids. For the Training and Education Program, we are committed to improving the participation of underrepresented minorities in biomedical research and in increasing awareness of health disparities among established cancer researchers. In this planning grant the two SUNY medical campuses will partner with CSHL to create an integrated doctoral certificate program Scholars in BioMedical Sciences in Cancer Health Disparities. This program is designed to engage doctoral students in translational medicine, particularly in cancer health disparities, by promoting in these students an understanding of the presentation, progression and treatment of diseases related to their area of thesis research. The track requires the addition of a clinical co-mentor to the usual student-basic science advisor team who will help guide the student's biomedical/clinical research and immerse the student in clinical experiences, vocabulary, and the overall culture of clinical research.

## **Project Narrative**

In the US, individuals of African descent are at higher risk for developing GI cancers (colorectal and pancreatic) and also exhibit higher mortality rates for these cancers compared to individuals of Caucasian descent. This grant will serve to build an integrative partnership between two SUNY medical campuses, Stony Brook and Downstate, and the NCI-designated Cancer Center at Cold Spring Harbor Laboratories to study racial and ethnic differences in GI cancer biology. Along with community education and outreach programs, this partnership will improve our ability to collect the under-represented minority (URM) biospecimens that are critical for research addressing the disparity of URM populations and GI cancers. By integrating the education and training resources of these three institutions, we will increase the recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies.

## Facilities

### Laboratories:

Stony Brook: Dr. Li and Dr. William's laboratories consist of adjacent wet bench bays totaling 8 benches in Gastroenterology Division open research space on the 17th floor of the Health Sciences Center building, which is immediately adjacent to the Stony Brook University Hospital. The lab is flanked by a biohazard tissue culture room for handling of human samples, and a walk-in cold room and by office spaces for Dr. Williams and the research nurse coordinator.

SUNY Downstate: Dr. Martello-Rooney's laboratory is housed within Division of Gastroenterology research space on the 8th floor of the Basic Science Building.

### Clinical:

Stony Brook: The Stony Brook Digestive Disorders Institute facilitates scheduling screening colonoscopies without first having a face-to-face consultation with a gastrointestinal specialist in select patients with stable health using highly trained bilingual patient navigators. The Stony Brook Medicine Endoscopy Unit, located within Stony Brook University Hospital, is a state-of-the-art procedural unit with 6 procedure rooms. The unit is recognized by the American Society for Gastrointestinal Endoscopy for promoting quality in endoscopy and has been recently expanded and updated to support current and future demand for our services. We are currently performing greater than 8,500 endoscopic procedures annually. The outpatient clinic is located 3.6 miles from the hospital and serves a diverse group of patients including indigent patients referred from neighborhood health clinics.

SUNY Downstate: SUNY Downstate Medical Center is one of the nation's leading urban medical centers, located in the East Flatbush section of Brooklyn, one of the country's most ethnically and culturally diverse neighborhoods within a Brooklyn community that has a minority population of over 50%. It operates two centers, the Center of Community Health Promotion and Wellness and the Brooklyn Health Disparities Center, which will play important roles in assisting with patient recruitment. The Center for Community Health Promotion and Wellness (established in 1996), participates in numerous community health promotion outreach activities in collaboration with School of Public Health, College of Nursing, College of Medicine reaching out to seniors, churches/faith groups, community based organizations, public officials, local school districts, and business entities reaching approx. 13,350 residents in the borough of Brooklyn. This center participates in over 100 community events in underserved communities each year and has a track record of successfully recruiting and screening patients. The screening program also provides resources for patient follow-up and scheduling for various programs. This avenue for patient identification and recruitment will be instrumental for recruitment of participants in this proposal. The Brooklyn Health Disparities Center is funded through the NIH P20 under the direction of the Principal Investigator's Drs. Moro Salifu (SUNY Downstate Medical Center) and Ruth Browne (Arthur Ashe Institute for Urban Health). It has an extensive network for recruiting participants into research protocols. The SUNY Downstate endoscopy unit performed 40 Brooklyn CSP colonoscopies last year.

### Computer

Stony Brook. The offices and laboratories of the investigative team are all equipped with personal computers which are linked via the university network. Drs. Bucobo, Denoya and Li are also linked to the Cerner electronic medical records in their academic and clinic offices. The Biomedical Informatics Department at Stony Brook University houses the following resources: The largest-memory machines, (Newton, Galileo, and Einstein) are Dell Poweredge T710s, with 16TB of hard drive storage, 144GB of RAM running at 800MHz, with 2 6-core Intel Xeon X5660 hyperthreaded 2.8GHz processors for a total of 12 cores. These are supported by a 45-disk, 135 terabyte high-speed BackBlaze \_le server, with a terabyte backup machine, and several

laboratory web servers. In addition, Stony Brook has committed to fund \$500k to develop a cluster computing facility which will consist of roughly twelve multi-core/multi-processor nodes with GPUs and a 100TB storage system to be housed in the Department of Computer Science

SUNY Downstate: The offices and laboratories of the investigative team are equipped with personal computers which are linked via the university network.

### **Office**

Stony Brook: Academic offices for the investigators are located in the Health Science Center Building.

SUNY Downstate: Academic offices are located in the Basic Science Building.

## **Equipment**

Stony Brook: - 80 C freezers, biohazard hoods, microfuge, PCR thermocycler, Agilent Bioanalyzer.

SUNY Downstate: Biohazard hood, microfuge.

Program Director/Principal Investigator (Last, First, Middle): CARETHERS, John M.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>JOHN M. CARETHERS, M.D.</b>	POSITION TITLE John G. Searle Professor of Internal Medicine Chair, Department of Internal Medicine		
eRA COMMONS USER NAME (credential, e.g., agency login) jcarethers			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Wayne State University	B.S.	1981-1985	Biological Sciences
Wayne State University	M.D.	1985-1989	Medicine
Massachusetts General Hospital	Residency	1989-1992	Internal Medicine
University of Michigan Hospitals	Fellowship	1992-1995	Gastroenterology

**A. Personal Statement**

I have >20 years experience in the field of colorectal cancer and genetics within gastroenterology, and know the importance of training the next generation of physician-scientists, with experience as a T32 director, fellowship director, division chief and department chair, coupled with the more than 50 trainees I have mentored. I have a vested interest in the field of cancer disparities, with experience as PI (current U01) and former co-PI of a U54 Comprehensive Cancer Center Partnership, Program Leader of the Reducing Cancer Disparities program at a comprehensive cancer center, and multiple publications regarding the approach to care and the biology of colorectal cancer among African Americans.

**B. Positions, Employment, and Honors**

1995-2001 Assistant Professor of Medicine in Residence, University of California, San Diego  
 2000-2004 Gastroenterology Fellowship Director, University of California, San Diego  
 2001-2005 Associate Professor of Medicine, University of California, San Diego  
 2002-2005 Chief, Gastroenterology Section, VA San Diego Healthcare System  
 2004-2009 Chief, Division of Gastroenterology, University of California, San Diego  
 2005-2009 Professor of Medicine (tenured), University of California, San Diego  
 2007-2010 Director, UCSD Gastroenterology NIH T32 Training Grant  
 2007-2009 Director, UCSD NIH Digestive Diseases Research Development Center (DDRDC)  
 2008-2009 co-Program Leader, Reducing Cancer Disparities, UCSD Comprehensive Cancer Center  
 2008-2012 co-PI, NCI U54 Comprehensive SDSU/UCSD Cancer Center Partnership  
 11/2009- John G. Searle Professor and Chairman, Dept. of Internal Medicine, University of Michigan

**Other Experience and Professional Memberships**

2000-2003 Editorial Board, *American Journal of Physiology: Gastrointestinal & Liver Physiology*  
 2002-2006 NIH CSR Gastrointestinal Cell and Molecular Biology Study Section (GCMB)  
 2006-2011 Board of Editors, *Gastroenterology*; Section Editor, *This Month in Gastroenterology*  
 2006-2008 National Commission on Digestive Diseases (appointed by Elias Zerhouni, M.D.)  
 2007-2012 AGA Council; Vice-Chair (07-09) and Chair (09-12) of Gastrointestinal Oncology Section  
 2009-2010 AGA Underrepresented Minorities Committee  
 2010-2014 University of Michigan Hospitals and Health Centers Executive Board (elected)  
 2011-2016 Senior Associate Editor, *Gastroenterology*  
 2012-2017 American Association of Physicians (AAP) Councilor (elected)  
 2014-2017 University of Michigan Medical School Executive Committee (elected)

**Honors**

Alpha Omega Alpha Honor Medical Society (1988); Commonwealth Fund Medical Research Fellow, National Medical Fellowships (1988); Henry J. Kaiser Family Foundation Award, National Medical Fellowships (1989); Franklin C. McLean Award, National Medical Fellowships (1989); UCSD Department of Medicine Graduating House Staff Teaching Award (1999); Fellow, American College of Physicians (FACP) (1999); Fellow,

Principal Investigator/Program Director (Last, First, Middle): CARETHERS, John M.

American College of Gastroenterology (FACG) (2001); UCSD Gastroenterology Fellows Excellence in Clinical Teaching Award (2004); Fellow, American Gastroenterological Association (AGAF) (2005); Western Association of Physicians (2006); UCSD School of Medicine Vice-Chancellor's Award for Mentoring Excellence (2006); American Society for Clinical Investigation (2008); American Association of Physicians (2011); Institute of Medicine, National Academy of Sciences (2012); American Clinical and Climatological Association (2014); Wayne State University School of Medicine Distinguished Alumni Award (2015)

### C. Selected peer-reviewed publications (in chronological order, from a total of >110)

1. **Carethers JM**, Hawn MT, Chauhan DP, Luce MC, Marra G, Koi M, Boland CR. Competency in mismatch repair prohibits clonal expansion of cancer cells treated with *N*-methyl-*N*-nitro-*N*-nitrosoguanidine. *J Clin Invest* 1996; **98**:199-206. PMC507417.
2. Zigman AF, Lavine JE, Jones MC, Boland CR, **Carethers JM**. Localization of Bannayan-Riley-Ruvalcaba syndrome gene to chromosome 10q23. *Gastroenterology* 1997; **113**:1433-1437. PMID: 9352843
3. **Carethers JM**, Hawn MT, Greenson JK, et al. Prognostic significance of allelic loss at chromosome 18q21 for stage II colorectal cancer. *Gastroenterology* 1998; **114**:1188-1195. PMID: 9609755
4. **Carethers JM**, Furnari FB, Zigman AF, Lavine JE, Jones MC, Graham GE, Teebi AS, Huang H-JS, Ha HT, Chauhan DP, Chang CL, Cavenee WK, Boland CR. Absence of *PTEN/MMAC1* germline mutations in sporadic Bannayan-Riley-Ruvalcaba syndrome. *Cancer Res* 1998; **58**:2724-2726. PMID: 9661881
5. **Carethers JM**, Chauhan DP, Fink D, Nebel S, Bresalier RS, Howell SB, Boland CR. Mismatch repair proficiency and *in vitro* response to 5-fluorouracil. *Gastroenterology* 1999; **117**: 123-131. PMID: 1038191
6. Yashiro M, **Carethers JM**, Laghi L, Saito K, et. al. Genetic pathways in the evolution of morphologically distinct colorectal neoplasms. *Cancer Res* 2001; **60**:2676-2683. PMID: 11289147
7. Huang SC, Lavine JE, Boland PS, Newbury RO, Kolodner R, Pham T-TT, Boland CR, **Carethers JM**. Germline characterization of early-aged onset of hereditary non-polyposis colorectal cancer. *J Pediatr* 2001; **138**:629-635. PMID: 11343035
8. Chang CL, Marra G, Chauhan DP, Ha HT, Chang DK, Ricciardiello L, **Carethers JM**, et. al. Oxidative stress inactivates the DNA mismatch repair system. *Am J Physiol Cell Physiol* 2002; **283**:C148-C154. PMID: 12055083
9. Ashkortab H, Smoot DT, **Carethers JM**, Rahmanian M, Kittles R, Vosgianian G, Doura M, Nidhiry E, Naab T, Momen B, Shakhani S, Giardiello FM. High incidence of microsatellite instability in colorectal cancer from African Americans. *Clinical Cancer Res* 2003; **9**:1112-1117. PMID: 12631615
10. **Carethers JM**, Smith EJ, Behling CA, Nguyen L, Tajima A, Doctolero RT, Cabrera BL, Goel A, Arnold CA, Miyai K, Boland CR. Use of 5-fluorouracil and survival in patients with microsatellite unstable colorectal cancer. *Gastroenterology* 2004; **126**: 394-401. PMID: 14762775
11. Jung B, Doctolero RT, Tajima A, Nguyen AK, Keku T, Sandler RS, **Carethers JM**. Loss of activin receptor type 2 protein expression in microsatellite unstable colorectal cancers. *Gastroenterology* 2004; **126**:654-659. PMID: 14988818
12. Goel A, Arnold CN, Niedzwiecki D, **Carethers JM**, Wasserman L, et al. Frequent inactivation of PTEN by promoter hypermethylation and its association with microsatellite instability-high (MSI-H) in sporadic colorectal cancers. *Cancer Res* 2004; **64**:3014-3021. PMID: 15126336
13. Tajima A, Hess M, Cabrera BL, Kolodner R, **Carethers JM**. The mismatch repair complex hMutS $\alpha$  recognizes 5-fluorouracil-modified DNA as a mechanism for chemosensitivity. *Gastroenterology* 2004; **127**:1678-1684. PMID: 15578504
14. Satia JA, Keku T, Galanko JA, Martin C, Doctolero RT, Tajima A, Sandler RS, **Carethers JM**. Diet, lifestyle, and genomic instability in the North Carolina Colon Cancer Study. *Cancer, Epidemiol, Biomarkers, and Prevention* 2005; **14**:429-436. PMID: 15734969
15. Ashktorab H, Smoot DT, Farzanmehr H, Fidelia-Lambert M, Momen B, Hyland L, Iacoso-Dononue C, **Carethers JM**, Goel A, Boland CR, Giardiello FM. Clinicopathological features and MSI in colorectal cancers from African Americans. *International Journal of Cancer* 2005; **116**:914-919. PMID: 15856472
16. **Carethers JM**. Unwinding the heterogeneous nature of hamartomatous polyposis syndromes. *JAMA* 2005; **294**:2498-2500. PMID: 16287964
17. Jung B, Smith EJ, Doctolero RT, Gervaz P, Alonso JC, Miyai K, Keku T, Sandler RS, **Carethers JM**. Influence of target gene mutation on survival, stage, and histology in sporadic microsatellite unstable colon cancers. *International Journal of Cancer* 2006; **118**:2509-2513. PMID: 16380996

Principal Investigator/Program Director (Last, First, Middle): CARETHERS, John M.

18. Beck SE, Jung BH, Fiorino A, Gomez J, Del Rosario E, Cabrera BL, Huang SC, Chow JYC, and **Carethers JM**. Bone morphogenetic protein signaling and growth suppression in colon cancer. *Am J Physiology GI & Liver Physiology* 2006; **291**:G135-G145. PMID: 16769811
19. Jung BH, Beck SE, Cabral J, Chau E, Cabrera BL, Fiorino A, Smith EJ, Bocanegra M, **Carethers JM**. *Activin type 2 receptor* restoration in MSI-H colon cancer suppresses growth and enhances migration with activin. *Gastroenterology* 2007; **132**:633-644. PMID: 17258738.
20. Beck SE, Jung B, Del Rosario E, Gomez J, **Carethers JM**. BMP-induced growth suppression in colon cancer cells is mediated by p21/WAF1 stabilization and modulated by RAS/ERK. *Cell Signal* 2007; **19**:1465-1472. PMID: 17317101
21. Beck SE, **Carethers JM**. BMP suppresses *PTEN* expression via RAS/ERK signaling. *Cancer Biol & Ther*, **6**:1313-1317, 2007. PMID: 18059158
22. Chow JYC, Quach KT, Cabrera BL, Cabral JA, Beck SE, **Carethers JM**. RAS/ERK modulates TGF $\beta$ -regulated *PTEN* expression in human pancreatic adenocarcinoma cells. *Carcinogenesis*; **28**:2321-2327, 2007. PMID: 17638924
23. Shin SK, Nagasaka T, Jung BH, Matsubara N, Kim WH, **Carethers JM**, Boland CR, Goel A. Epigenetic and genetic alterations in Netrin-1 receptors UNC5C and DCC in human colon cancer. *Gastroenterology*; **133**:1849-1857, 2007. PMID: 18054557
24. Chow JYC, Dong H, Quach KT, Nguyen PNV, Chen K, **Carethers JM**. TGF $\beta$  mediates *PTEN* suppression and cell motility through calcium-mediated PKC $\alpha$  activation in pancreatic cancer cells. *Am J Physiol Gastrointest Liver Physiol*, **294**:G899-G905, 2008. PMID: 18239055
25. Grady WM and **Carethers JM**. Genomic and epigenetic instability in colorectal cancer pathogenesis. *Gastroenterology* **135**:1079-1099, 2008. PMC2866182.
26. Chow JYC, Cabral JA, Chang J, **Carethers JM**. TGF $\beta$  modulates *PTEN* expression independently of SMAD signaling for growth proliferation in colon cancer cells. *Cancer Biol & Ther* **7**:1694-1699, 2008. PMC2820113
27. Chung H, Young DJ, Lopez C, Le T-AT, Lee JK, Ream-Robinson D, Huang SC, **Carethers JM**. Mutation rates of *TGFB2* and *ACVR2* coding microsatellites in human cells with defective DNA mismatch repair. *PLoS ONE* **3**:e3463, 2008. PMC2565065.
28. Jung BH, Gomez J, Chau E, Cabral J, Lee JK, Anselm A, Slowik P, Ream-Robinson D, Messer K, Sporn J, Shin SK, Boland CR, Goel A, **Carethers JM**. Activin signaling in microsatellite stable (MSS) colon cancers is disrupted by a combination of genetic and epigenetic mechanisms. *PLoS ONE*, **4**:e8308, 2009. PMC2789408.
29. Chow JYC, Ban M, Wu HL, Nguyen F, Huang M, Chung H, Dong H, **Carethers JM**. TGF $\beta$  downregulates *PTEN* via activation of NF- $\kappa$ B in Pancreatic Cancer Cells. *Am J Physiol Gastrointest Liver Physiol*, **298**:G275-82, 2010. PMID: 19940030
30. Chung H, Lopez CG, Young DJ, Ream-Robinson D, Cabrera BL, **Carethers JM**. Flanking sequence specificity determines coding microsatellite heteroduplex and mutation rates with defective DNA mismatch repair. *Oncogene* **29**:2172-2180, 2010. PMID: 20140012
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32. Ghosh P, Beas AO, Bornheimer SJ, Garcia-Marcos M, Forry EP, Johansson C, Ear J, Jung BH, Cabrera B, **Carethers JM**, Farquhar MG. A Gi-G1V molecular complex binds epidermal growth factor receptor and determines whether cells migrate or proliferate. *Mol Biol Cell* **21**:2338-54, 2010. PMC2893996.
33. Deveraj B, Lee A, Cabrera BL, Miyai K, Luo L, Ramamoorthy S, Keku T, Sandler RS, McGuire K, **Carethers JM**. Relationship of EMAST and microsatellite instability among patients with rectal cancer. *J Gastrointest Surg* **14**:1521-8, 2010. PMC2943582.
34. Lee S-Y, Chung H, Deveraj B, Iwaizumi M, Han HS, Hwang D-Y, Seong MK, Jung BH, **Carethers JM**. Elevated microsatellite alterations at selected tetranucleotide repeats are associated with morphologies of colorectal neoplasia. *Gastroenterology* **139**:1519-1525, 2010. PMC2967646.
35. Chung H, Chaudhry J, Lopez, CG, **Carethers JM**. Cyclin E and histone H3 are regulated by 5-fluorouracil in a DNA mismatch repair-dependent manner. *Cancer Biol & Ther* **10**:1147-1156, 2010. PMC3230292.

Principal Investigator/Program Director (Last, First, Middle): CARETHERS, John M.

36. Dong H, Shim K-N, Li J, Estrema C, Orneles T, Nguyen F, Liu S, Ramamoorthy S, Ho S, **Carethers JM**, Chow JYC. Molecular mechanisms underlying  $\text{Ca}^{2+}$ -mediated motility of human pancreatic duct cells. 2010. *Am J Physiol Cell Physiol* **299**:C1493-1503, 2010. PMC3006328.
37. Huang SC, Lee JK, Smith EJ, Doctolero R, Tajima A, Beck SE, Weidner N, **Carethers JM**. Evidence for an hMSH3 defect in familial hamartomatous polyps. *Cancer* **117**:492-500, 2011. PMC3005073
38. Garcia-Marcos M, Jung BH, Ear J, Cabrera BL, **Carethers JM**, Ghosh P. The expression of GIV/Girdin, a metastasis-related protein, predicts patient survival in colon cancer. *FASEB J* **25**:590-599, 2011. PMC3023389
39. Iwaizumi M, Tseng-Rogenski S, **Carethers JM**. DNA mismatch repair proficiency executing 5-fluorouracil cytotoxicity in colorectal cancer cells. *Cancer Biol Ther* **12**:756-764, 2011. PMC3367669
40. Tajima A, Iwaizumi M, Tseng-Rogenski S, Cabrera BL, **Carethers JM**. Both hMutS $\alpha$  and hMutS $\beta$  complexes participate in 5-fluorouracil cytotoxicity. *PLoS ONE*, **6**:e28117, 2011. PMC3229514
41. Lee S-Y, Miyai K, Han HS, Hwang D-Y, Seong MK, Chung H, Jung BH, Devaraj B, McgGuire KL, **Carethers JM**. Microsatellite instability, EMAST, and morphology associations with T cell infiltration in colorectal neoplasia. *Dig Dis Sci*, **57**:72-8, 2012. PMC3245369
42. Chung H, Chaudhry J, Lai JF, Young DJ, **Carethers JM**. Flanking nucleotide specificity for DNA mismatch repair-deficient frameshifts within *Activin Receptor 2 (ACVR2)*. *Mutat Res*, **729**:73-80, 2012. PMC3237829
43. Ayanian JZ and **Carethers JM**. Bridging Behavior and Biology to Reduce Socioeconomic Disparities in Colorectal Cancer Risk. *J Natl Cancer Inst* **104**:1343-1344, 2012. PMCID: pending
44. Tseng-Rogenski S, Chung H, Wilk MB, Zhang S, Iwaizumi M, **Carethers JM**. Oxidative stress induces nuclear-to-cytosol shift of hMSH3, a potential mechanism for EMAST in colorectal cancer cells. *PLoS ONE* **7**:e50616, 2012. PMC3511561
45. Iwaizumi M, Tseng-Rogenski S, **Carethers JM**. Acidic tumor microenvironment downregulates hMLH1 but does not diminish 5-fluorouracil chemosensitivity. *Mutat Res* **747-748**:19-27, 2013. PMC3770844
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47. **Carethers JM**. DNA testing and molecular screening for colon cancer. *Clin Gastroenterol Hepatol* **12**:377-381, 2014. PMCID: PMC4151968
48. **Carethers JM**. Differentiating Lynch-like from Lynch syndrome. *Gastroenterology* **146**:602-604, 2014. PMCID: PMC4134259
49. **Carethers JM**, Murali B, Yang B, Doctolero RT, Tajima A, Basa R, Smith EJ, Lee M, Janke R, Ngo T, Tejeda R, Ji M, Kinseth M, Cabrera BL, Miyai K, Keku TO, Martin CF, Galanko JA, Sandler RS, McGuire KL. Influence of race on microsatellite instability and CD8<sup>+</sup> T cell infiltration in colon cancer. *PLoS ONE* **9**:e100461, 2014. PMCID: PMC4067325
50. **Carethers JM**. Screening for colorectal cancer in African Americans: Determinants and rationale for an earlier age to commence screening. *Dig Dis Sci* 2015. (in press) PMCID: pending
51. Tseng-Rogenski S, Hamaya Y, Choi D, **Carethers JM**. Interleukin 6 alters localization of hMSH3, leading to DNA mismatch repair defects in colorectal cancer cells. *Gastroenterology* 2015. (in press) PMCID: pending

#### D. Research Support ongoing or completed during the last three years

##### R01 DK067287 Carethers (PI)

09/1/05 to 08/31/16

NIH/NIDDK

Microsatellite Instability and the DNA Mismatch Repair System

**Major goals:** To determine the role and expression of the DNA mismatch repair protein hMSH3 in preventing mutation of human DNA at microsatellite sequences.

##### U01 CA162147 Carethers (PI)

09/01/12 to 08/31/17

Inflammatory Differentiation of Colorectal Cancer among African Americans

**Major goals:** To evaluate the role of mismatch repair dysfunction and immune and cytokine profiles within colorectal cancers from diverse populations.

Principal Investigator/Program Director (Last, First, Middle): Baines, Antonio, T.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Baines, Antonio Thomas</b>	POSITION TITLE Associate Professor of Biology and the Cancer Research Program		
eRA COMMONS USER NAME			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Norfolk State University	B.S.	1995	Biology
University of Arizona	Ph.D.	2001	Pharmacology/ Toxicology
University of North Carolina at Chapel Hill	Postdoc	2006	Pharmacology

**A. Personal Statement**

I have been interested in molecular targeted therapy of pancreatic cancer for almost 8 years since completion of my postdoc studying oncogenic Ras signaling in pancreatic cancer under Dr. Channing Der. The overall focus of our cancer biology research program is to discover novel molecular targets in cancer, especially pancreatic cancer, which can be targeted by potential cancer therapeutics. We want to understand the role of these molecular targets in the development and progression of normal cells transforming into cancer cells of the pancreas. Most recently, we have become interested in molecular targets that are involved in drug resistance of pancreatic cancer to gemcitabine. Also, we have an interest in the health disparity seen with pancreatic cancer. We look forward to investigating the underlying role biology may contribute to the increased incidence and worse prognosis observed in certain populations.

**B. Positions and Honors****Positions and Employment**

2006- Assistant Professor of Biology & the Cancer Research Program, J. L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, North Carolina

2008- Adjunct Assistant Professor of Pharmacology, School of Medicine, UNC-Chapel Hill, Chapel Hill, North Carolina

2011-2012 Consultant, Jasco Pharmaceuticals

2013- Associate Professor of Biology & the Cancer Research Program, J. L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, North Carolina

2013- Adjunct Associate Professor of Pharmacology, School of Medicine, UNC-Chapel Hill, Chapel Hill, North Carolina

Principal Investigator/Program Director (Last, First, Middle): Baines, Antonio, T.

- 2014- Member, Curriculum in Toxicology, Graduate School, UNC-Chapel Hill, Chapel Hill, North Carolina
- 2014 Consultant, Clarion Healthcare, LLC

### **Professional Memberships and Selected Experiences**

- 1997- Society of Toxicology
- 1997- American Association for Cancer Research
- 2011 *Ad Hoc* Reviewer, NIH Molecular and Integrative Signal Transduction (MIST) Study Section
- 2011 Reviewer, European Journal of Cancer
- 2012- HHMI Grant EXROP Study Section
- 2015 *Ad Hoc* Reviewer, NIH Cancer Drug Development and Therapeutics (CDDT) Study Section

### **Selected Honors and Presentations**

- 2006 Invited Seminar Speaker, Gastroenterology Division Research Conference, Duke University Medical Center, Durham, NC
- 2007 Invited Seminar Speaker, Department of Pharmacology Seminar Series, UNC-Chapel Hill, Chapel Hill, NC
- 2011 Society of Toxicology-Toxicologists of African Origin (TAO) Mentor/Educator Award
- 2012 American Association for Cancer Research Minority-Serving Institution Faculty Scholar Awardee
- 2012 Invited Seminar Speakers – Department of Pharmacology and Toxicology– School of Medicine, Indiana University, Indianapolis, IN; Department of Environmental and Molecular Toxicology – NC State University, Raleigh, NC
- 2013 Invited Seminar Speaker – Pharmacology and Toxicology Division – University of Missouri-Kansas City, Kansas City, MO
- 2013 Invited Seminar Speaker – Department of Biology – Massachusetts Institute of Technology (MIT), Boston, MA
- 2014 Invited Seminar Speaker - Eppley Cancer Institute, University of Nebraska Medical Center, Omaha, NE
- 2014 Invited Seminar Speaker – Tolero Pharmaceuticals, Lehigh, UT

### **C. Selected Publications**

1. Sauer JM, Hooser SB, Badger DA, **Baines AT**, Sipes IG. (1995) Alterations in chemically induced tissue injury related to all-trans retinol pretreatment in rodents. *Drug Metabolism Reviews* 27(1&2):299-323.
2. Sauer JM, Waalkes MP, Hooser SB, **Baines AT**, Kuester RK, Sipes IG. (1997) Tolerance induced by all-trans-retinol to the hepatotoxic effects of cadmium in rats: role of metallothionein expression. *Toxicology and Applied Pharmacology* 143:110-119.
3. **Baines AT**, Holubec H, Basye JL, Thorne P, Bhattacharyya AK, Spallholz J, Shriver B, Cui H, Roe D, Clark LC, Earnest DL, Nelson MA. (2000) The effects of dietary selenomethionine on polyamines and azoxymethane-induced aberrant crypts. *Cancer Letters* 160:193-198.
4. Lim, K.-H., **Baines, A.T.**, Fiordalisi, J.J., Shipitsin, M., Feig, L.A., Cox, A.D., Der, C.J., and Counter, C.M.: (2005) Activation of RalA is critical for Ras-induced tumorigenesis of human cells. *Cancer Cell* 7:533-545. [PMC15950903]

Principal Investigator/Program Director (Last, First, Middle): Baines, Antonio, T.

5. **Baines, A.T.**, Lim, K.-H., Shields, J.M., Lambert, J.M., Counter, C.M., Der, C.J., and Cox, A.D.: Use of retrovirus expression of interfering RNA to determine the contribution of activated K-Ras and Ras effector expression in human tumor cell growth. Methods in Enzymology. Vol. 407, pp. 556-74, 2005.
6. Xu, D., Allsop, S.A., Witherspoon, S.M., Snider, J.L., Yeh, J.J., Fiordalisi, J.J., White, C.D., Williams, D., and **Baines, A.T.**: (2011) The oncogenic kinase Pim-1 is modulated by K-Ras signaling and mediates transformed growth and radioresistance in human pancreatic ductal adenocarcinoma cells. *Carcinogenesis*, 32(4):488-95. [PMC3066419]
7. **Baines, A.T.**, Xu, D., and Der, C.J.: Inhibition of Ras for cancer treatment: the search continues. Future Medicinal Chemistry, 1787-1808, 2011.
8. Xu, D., Cobb, M., Gavilano, L., Sam Witherspoon, S.M., Williams, D., White, C.D., Taverna, P., Bednarski, B., Hong Kim, H.J., Baldwin, A., and **Baines, A.T.**: (2013) Inhibition of oncogenic Pim-3 kinase modulates transformed growth and chemosensitizes pancreatic cancer cells to gemcitabine. *Cancer Biology & Therapy*, 14:6, 1-10. [PMC3813565]

#### D. Selected Research Support

NCCU/UNC-Lineberger U54 Partnership in Cancer Research Grant-NCI 08/2013-08/2015  
 "Identification of the Pim kinome in pancreatic cancer"  
 Role: Co-Investigator

Jasco Pharmaceuticals Collaborative Grant, "Pim kinase inhibitors in pancreatic cancer"  
 01/11-07/12  
 Role: PI

Duke-NCCU STEM Partnership Grant, "The role of Pim-1 kinase as a novel molecular target in pancreatic cancer" 09/01/08-11/30/09  
 Role: Co-Investigator

NCI/NIGMS MBRS Support of Competitive Research (SCORE) Pilot Project Award (SC2), entitled "The role of Pim kinases as a novel molecular target in pancreatic cancer" 08/01/08-07/31/12  
 Role: PI

Academy of Applied Science and the Army Research Office; Support high school students conducting research during the summers 2008-  
 Role: Co-Investigator

NCCU-BBRI/UNC-Lineberger Partnership in Cancer Research Pilot Grant, "Molecular targets in pancreatic cancer" 10/14/06-04/30/08  
 Role: Co-Investigator

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Fraser- White, Marilyn	POSITION TITLE Deputy Director		
eRA COMMONS USER NAME (credential, e.g., agency login) Mwhite30			
EDUCATION/TRAINING ( <i>Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.</i> )			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
City University of New York at Brooklyn College	BA	02/94	Chemistry
Spartan Health Sciences University School of Medicine	MD	04/00	Medicine

### A. Personal Statement

My experience in conducting community based research, as part of a community-based organization (Arthur Ashe Institute for Urban Health) with long-standing relationships within the community, as well as my leadership roles in the Brooklyn Health Disparities Center will be important to my role in an advisory capacity. In addition to my role as the Deputy Executive Director for the Arthur Ashe Institute, I serve as the Director of the Community Engagement Core of the NIH-NIMHD funded Brooklyn Health Disparities Center, a partnership between the SUNY Downstate Medical Center, the Arthur Ashe Institute for Urban Health, and the Office of the Brooklyn Borough President. In this capacity, my responsibilities include coordinating and supervising the development and implementation of a health disparities curriculum for high school students as well as a curriculum for community leaders to increase their capacity to conduct research. As part of a team of researchers working on a CDC funded project to develop a barbershop based HIV/AIDS risk reduction intervention for African American men, I have supervised the recruitment and formative phase of the project, and have collaborated with other investigators to develop the training modules for the intervention. I have also served as the principal investigator for a grant, funded by the New York University – Clinical & Translational Science Institute, to develop and pilot a cardiovascular disease (CVD) risk reduction intervention to train salon stylists to deliver heart health messages, including stress reduction messages, to their customers. I have coordinated many of the Institute's outreach programs, including the federally funded programs, and was instrumental in developing the Institute's salon and barbershop based programs into behavioral health intervention models. I have also served as a co-investigator for the Institute's ACCESS program to increase access to health and social resources for formerly incarcerated individuals and their families. As an NIH LRP award recipient, I conducted preliminary work to assess CVD risk factors among formerly incarcerated Black men. Additionally, I served as part of an investigative team of researchers to develop training curricula on various topics including cardiovascular disease, cancer (breast, prostate and colorectal), diabetes, HIV/AIDS, health disparities and community based participatory research. Most recently, I was the recipient of the Fulbright Research Specialist award. Given my vast experience in developing and conducting community health disparities intervention programs and leading the community engagement efforts of the Institute and the Brooklyn Health Disparities Center, I am well prepared to serve as a member of the advisory board.

### B. Positions and Honors.

#### Positions and Employment

1994-1996	<i>Public Health Advisor</i> , New York City Department of Health, Bureau of Tuberculosis Control (Regulatory Affairs), New York, NY,
2000-2001	<i>Outreach Coordinator/ Program Director (Acting)</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2001-2004	<i>Research Manager</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2003-present	<i>Instructor</i> , Health Science Academy (Arthur Ashe Institute)
2004-2012	<i>Associate Director, Research &amp; Training</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2007	<i>Acting Deputy Director</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2012-present	<i>Deputy Director</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY

### **Awards/ Honors**

Steven Biko Memorial Scholarship (1988)  
Minority Access to Research Careers (MARC) Fellowship (1988-1990)  
Sigma-Xi Rudin Fellowship Award (1990)  
SIPID Scholar (2008)  
Project Interchange Alumni (2008)  
Health Award (New York State Association of Black & Puerto Rican Legislators, Inc.) (2011)  
Extraordinary Women of Downstate Award (2012)  
NIH Loan Repayment Program award recipient (2012-2014)  
New York State Department of Health – Commissioner's Special Recognition Award (2013)  
Fulbright Research Specialist Fellowship Award (2013)  
Innovator Award – Bedford Stuyvesant Family Health Center (2014)

### **C. Contribution of Science**

#### **1. Development of Culturally Tailored Interventions**

I have worked closely with members of the community and faculty at various institutions to develop and implement culturally tailored curricula on various health issues such as prostate cancer, HIV/AIDS and cardiovascular disease.

- a. Brown N, Naiman P, Homel P, Fraser-White M, Clare R, Browne R. (2006). Assessment of preventive health knowledge and behaviors of African-American and Afro-Caribbean women in urban settings. *J Natl Med Assoc.*, 98(10), 1644-1651. PMID: PMC2569737
- b. Fraser M, Brown H, Homel P, Macchia RJ, LaRosa J, Clare R, Davis-King D, Collins P, Samuel T, Macalino G, Browne R. (2009) Barbers as Lay Health Advocates – Developing a Prostate Cancer Curriculum. *J Natl Med Assoc.*, 101(7), 690-697. PMID: 19634590
- c. Brown, N., Vaughn, N.A., Lin, A.J., Browne, R., White, M., & Smith, P. (2011) Healthy Families Brooklyn: Working with Health Advocates to Develop a Health Promotion Program for Residents Living in New York City Housing Authority Developments. *J. Community Health*, 36(5), 864-873. PMID: 21400120
- d. Boutin-Foster C, George K, Samuel T, Fraser-White M, Brown H. (2008). Training Community Health Workers to be Advocates for Health Promotion: Efforts Taken by a Community-Based Organization to Reduce Health Disparities in Cardiovascular Disease. *Journal of Community Health*, 33(2), 61-68. PMID:18058210

#### **2. Replication of Innovative Science Models**

As part of an investigative team of researchers, I have worked on the replication of the Institute's community outreach efforts in non-traditional settings. As a recipient of a Fulbright Research Specialist award, I developed and implemented a program on climate change and public health in collaboration with the University of the West Indies. I am currently working as a co-investigator on a pilot project across universities in the West Indies and various State Universities of New York to assess cardiovascular disease risk in individuals of Caribbean descent in New York and those in their native Caribbean countries.

- a. Browne R, Vaughn NA, Siddiqui N, Brown N, Delmoor E, Randleman P, Randleman S, Gonzalez L, Lewis J, Lourie R, Foster G, Brown H, Fraser-White M, Banks S. (2009) Community-Academic Partnerships: Lessons Learned from Replicating a Salon-Based Health Education and Promotion Program. *Progress in Community Health Partnerships: Research, Education and Action*, 3(3), 241-248. PMID: 2020822
- b. Henry KR, Fraser-White M, Roberts CR, Wilson TE, Morgan R, Brown H, Shaw R, Jean-Louis G, Graham YJ, Brown C, Browne R. (2012) Engaging Minority High School Students as Health Disparities Interns: Findings and Policy Implications of a Summer Youth Pipeline Program. *J Natl Med Assoc.*, 104 (9, 10), 412-419

#### **3. Community Engaged Research**

One of my contributions to science has been my extensive work in the community, in developing, implementing and assessing interventions that are focused on addressing health disparities and reducing risk factors for disease.

- a. Clark, L, Browne, R., Kokolis, R., White, M., Morales, S.: Health Disparities and Cardiovascular Disease, in Clark, LT (ed.): Cardiovascular Disease and Diabetes: Modern Management. New York, McGraw-Hill, 2006; p 506
- b. Wilson T, Fraser-White M, Feldman J, Homel P, Wright S, King G, Coll B, Banks S, Davis-King D, Price M, Browne R. (2008). Hair salon stylists as breast cancer prevention lay health advisors for African American and Afro-Caribbean women. Journal of Health Care for the Poor and Underserved, 19, 216-226. PMID:18263997
- c. Wilson TE, Fraser-White M, Williams KM, Pinto A, Agbetor F, Camilien B, Henny K, Browne RC, Gousse Y, Taylor TN, Brown H, Taylor RD, Joseph MA. Barbershop Talk with Brothers: Using Community-Based Participatory Research to Develop and Pilot Test a Program to Reduce HIV Risk among Black Heterosexual Men. AIDS Educ Prev 2014 Oct;26(5):383-97
- d. Taylor TN, Joseph MA, Henny KD, Pinto AR, Agbetor F, Camilien B, Williams KM, Browne RC, White M, Gousse Y, Brown H, Taylor RD, Wilson TE. Perceptions of HIV risk and explanations of sexual risk behavior offered by heterosexual Black male barbershop patrons in Brooklyn, NY. Journal of Health Disparities Research and Practice [forthcoming].

#### 4. Community Based Participatory Research (CBPR)

The importance of fostering community-academic partnerships is essential to the success of research efforts that are focused on eliminating health disparities. I have had the opportunity to develop and implement training activities for community based organizations and faculty on CBPR. I have worked closely with CBO's on increasing the capacity of community numbers to conduct research

- a. Roberts CB, Browne R, Wilson TE, Morgan R, Brown H, Shaw R, Jean-Louis G, Brown C, Fraser-White M. Lessons Learned from Building an Infrastructure for Community-Based Participatory Research. International Public Health Journal [in press]
- b. Henry KR, Fraser-White M, Roberts CR, Wilson TE, Morgan R, Brown H, Shaw R, Jean-Louis G, Graham YJ, Brown C, Browne R. (2012) Engaging Minority High School Students as Health Disparities Interns: Findings and Policy Implications of a Summer Youth Pipeline Program. J Natl Med Assoc., 104 (9, 10), 412-419

### 5. Research Support

#### Ongoing Research Support

HHSN276201400887P

National Library of Medicine Fraser-White (PI)

09/30/14 – 09/29/15

"AAIUH mHealth HIV/AIDS Risk Reduction Initiative"

The goal of the project is to facilitate and improve access to NLM's HIV/AIDS medical information and educational resources for high-need individuals, caregivers, family, friends and other community members.

Role: Director

P1-12-001

Jensen, Levine (PIs)

07/01/12 – 06/30/14

PCORI

"Mobile Apps (MAPPS): Patient & Caregiver Attitudes, Behaviors & Knowledge"

The aim of this collaborative project is to explore the needs, attitudes, knowledge, and behavior toward M-tech for health management within the model of stroke, as stroke survivors and their caregivers require continuous monitoring and informational updates.

Role: Co-investigator

1P20MD006875-01

Browne, Salifu (PIs)

06/14/12 – 01/31/17

NIH - NIMHD

"Brooklyn Health Disparities Center – Community Engagement"

The goal of this grant is to strengthen the capacity of the Brooklyn Health Disparities Center through its community engagement core by developing and implementing a health disparities curriculum for high school students and a curriculum on community based participatory research to increase the capacity of local community based organizations.

Role: Director – Community Engagement

NIH-Loan Repayment Program (LRP) Fraser-White (PI) 2012-2014

“ACCESS Project for Formerly Incarcerated Individuals”

The goal of this grant is to assess cardiovascular disease risk factors among formerly incarcerated individuals.

Role: Loan Repayment Program Participant

### **Completed Research Support**

New York Department of Health 03/15/12-07/15/12

*Communities of Color Condom Distribution Project*

The goal of this project is to raise awareness about HIV/AIDS among minorities, through distribution of condoms and information on HIV/AIDS (i.e. brochures, pamphlets and video documentary), in non-traditional venues such as barbershops and salons in Central Brooklyn.

Role: Director

1UL1RR029893 White (PI) 03/29/10-03/28/11

NYU-HHC CTSI

*“Heart of a Woman”*

The goal of this grant is to pilot a cardiovascular disease curriculum to train community- based professional stylists, as messengers, to deliver heart health messages to their customers to promote healthy behaviors that will reduce risk of cardiovascular disease in minority women.

Role: Principal Investigator

1P20MD005092-01 Brown, Browne, Wilson (PIs) 09/30/09 – 07/31/12

NIH - NCMHD

*“Brooklyn Health Disparities Center – Community Engagement”*

The goal of this grant is to strengthen the capacity of the Brooklyn Health Disparities Center through its community engagement core by developing and implementing a health disparities curriculum for high school students and a curriculum on community based participatory research to increase the capacity of local community based organizations.

Role: Director – Community Engagement

1 UR6 PS000691-01, Wilson (PI) 09/01/07 – 02/29/12

CDC

*“Reducing HIV Heterosexual Risk among African-American Men”*

The overall goal of this project is to develop a program that will reach heterosexual men in barbershops serving communities with high HIV morbidity and AIDS related mortality;

Role: Co-Investigator

Empire BlueCross BlueShield Browne (PI) 01/01/11-12/31/11

*“Heart of a Woman”*

The goal of this grant is to implement a cardiovascular disease intervention program in which professional salon stylists are trained to deliver heart health messages to their customers to promote healthy behaviors that will reduce risk of cardiovascular disease in minority women.

Role: Co-Investigator

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Samuel Ryu M.D.</b>		POSITION TITLE <b>Professor &amp; Chair, Dept of Radiation Oncology</b>	
eRA COMMONS USER NAME (credential, e.g., agency login) <b>Saryu1</b>			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Kyungpook University School of Medicine, Korea	M.D.	1982	Medicine
Kyungpook University Graduate School, Korea	M.S.	1988	Radiology
Yonsei and Kyungpook University Hospital, Korea	Residency	1986-1989	Radiation Oncology
Henry Ford Hospital, Detroit, MI	Post-doc	1991-1993	Tumor and Radiation Biology
Henry Ford Hospital, Detroit, MI	Residency	1993-1996	Radiation Oncology

**A. Personal Statement:**

As Chair of the Department of Radiation Oncology, I have a strong commitment to the diagnosis, treatment and research of GI cancers. In fact our department is launching a new clinical protocol for treating unresectable/borderline resectable pancreatic adenocarcinoma with SBRT/chemotherapy. My department is consequently very interested in the development of pancreatic organoids from EUS-FNB biopsies, which may serve as a model for assessing the most effective therapy for individual cases of pancreatic cancer.

**B. Positions and Honors:**

1989-1993	Assistant Professor, Radiation Oncology, Kyungpook University Hospital, Korea
1996-1999	Assistant Professor of Radiation Oncology, Upstate Medical Center, Syracuse, NY
1999-2014	Senior Staff, Radiation Oncology, Henry Ford Hospital, Detroit, Michigan
2000-2014	Director, Center for Radiosurgery, Henry Ford Hospital
2005-2014	Leader, Neuro and Spine Oncology/ Spine Tumor Board, Henry Ford Health System
2010-2011	NCI Study Section, Clinical Studies Special Emphasis Panel
2010-	Founding Editor-in-chief, Journal of Radiosurgery and SBRT
2013-2015	President, International Stereotactic Radiosurgery Society
2014-	Professor and Chair, Radiation Oncology, Stony Brook University School of Medicine
2014-	Deputy Director for Clinical Affairs, Stony Brook Cancer Center

**C. Peer-reviewed Publications: (selected)**

- Kleinberg L, Supko JG, Mikkelsen T, Blakeley JO, Stevens G, Ye X, Desideri S, **Ryu S**, Desai B, Giranda VL, Grossman SA. Phase I adult brain tumor consortium (ABTC) trial of ABT-888 (veliparib), temozolomide (TMZ), and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM) including pharmacokinetic (PK) data. *Journal of Clinical Oncology*. 2013;31(15).
- Kim EY, Yechieli RL, Kim JK, Mikkelsen T, Kalkanis S, Rock JP, **Ryu S**. Patterns of Failure after Radiosurgery to different target volumes of enhancing lesion only versus enhancing lesion and FLAIR abnormality for recurrent Glioblastoma Multiforme. *Journal of Neuro-oncology* 116:291-297. 2014 doi: 10.1007/s11060-013-1290-1294. Epub 2013 Oct 31. PMID: 24173682
- Ryu S**, Ryken T, Olson J, Kalkanis S. The role of radiotherapy in the management of progressive glioblastoma multiforme. *Journal of Neuro-oncology* 18(3):489-99, 2014. doi: 10.1007/s11060-013-1337-6. Epub 2014 Apr 12.
- Zhao B, Jin JY, Wen N, Huang Y, Siddiqui MS, Chetty I, **Ryu S**. Prescription to 50-75% isodose line may be

Program Director/Principal Investigator (Last, First, Middle):

- optimum for linear accelerator based radiosurgery of cranial lesions. *Journal of Radiosurgery and SBRT* 2014
5. Jin JY, Huang Y, Brown SL, Movsas M, Chetty IJ, **Ryu S**, Kong FM. Radiation dose-fractionation effects in spinal cord: comparison of animal and human data. *Physics in Medicine and Biology* 2014 (in print)
  6. Huang Y, Chin K, Robbins J, Kim J, Li, H, Amro H, Chetty IJ, Gordon J, **Ryu S**. Radiosurgery of multiple brain metastases with single-isocenter dynamic conformal arcs (SIDCA). *Radiotherapy and Oncology* 112(1):128-32, 2014. doi: 10.1016/j.radonc.2014.05.009. Epub 2014 Jul 2
  7. Chin K, Ryu S. The Use of Jaw Tracking in Intensity Modulated and Volumetric Modulated Arc Radiotherapy for Spine Stereotactic Radiosurgery. *Practical Radiation Oncology* 2014 PRACTICALRADONC-D-14-00138R1
  8. Bellon M, Siddiqui MS, Ryu S, Chetty I. The effect of longitudinal CT resolution and pixel size (FOV) on target delineation and treatment planning in stereotactic radiosurgery. *Journal of Radiosurgery and SBRT* 2014
  9. Robbins JR, Kim SR, Kalkanis S, Cogan C, Rock J, Rosenblum M, Kim JH, **Ryu S**. Stereotactic radiosurgery in the multidisciplinary management of large (target volume  $\geq 20$  cc or  $\geq 3$  cm in diameter) brain metastases. *Journal of Neurosurgery* 2014
  10. Fisher BJ, Hu C, Macdonald DR, Lesser GJ, Coons S, Brachman DG, **Ryu S**, Werner-Wasik M, Bahary JP, Liu J, Chakravati A, Mehta MP. Phase II study of a Temozolomide-based chemoradiotherapy regimen for high-risk low-grade gliomas: Results of RTOG 0424. *International Journal of Radiation Oncology Biology Physics* 91(3): 497-504, 2015
  11. Lo SS, Ryu S, Chang EL, Galanopoulos N, Jones J, Kim EY, Kubicky CD, Lee CP, Rose PS, Sahgal A, Sloan AE, The BS, Traughber BJ, Poznak CV, Vassil, AD. American College of Radiology ACR Appropriateness Criteria® Expert Panel on Radiation Oncology–Bone Metastases: Metastatic epidural spinal cord compression and recurrent spinal metastasis. *Journal of Palliative Medicine* 2015 (in Print)
  12. Thibault I, Lo SS, Chang EL, Sheehan J, Ahluwalia MS, Guckenberger M, Sohn MJ, Ryu S, Foote M, Muacevic A, Soltys SG, Chao S, Gerszten P, Lis E, Yu E, Bilsky M, Fisher C, Schiff D, Fehlings MG, Ma L, Chang S, Chow E, Parelukar W, Vogelbaum M. Challenges Determining Response after Stereotactic Body Radiotherapy for Spinal Metastases and Review of Current Practices: Part 1 of a First Report from the Spine Response Assessment in Neuro-Oncology (SPANO) Group. *Lancet Oncology* 2015 (under review)
  13. Redmond KJ, Robertson S, Lo SS, Soltys S, **Ryu S**, McNutt T, Chao S, Barani I, Yamada J, Ghia A, Chang EL, Sheehan J, Sahgal A. Consensus Contouring Guidelines for Post-Operative Spine Stereotactic Body Radiation Therapy. *ISRS* 2015
  14. **Ryu S**, Yoon H, Stessin A, Rosiello A, Gutman F, Davis R. Contemporary Treatment with Radiosurgery for Spine Metastasis and Spinal Cord Compression in 2015. *Radiation Oncology Journal* 2015 (in print)

## D Research Support

### ACTIVE

2009- RTOG-0631 Phase II/III study of spine radiosurgery for localized spine metastasis. (Role: National P.I. and Study chair) -- U10 CA 21661-325 (RTOG), U10 CA37422-21 (CCOP)

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Minsig Choi MD</b>	POSITION TITLE <b>Associate Professor of Medicine</b>		
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of the Philippines, Metro Manila, Philippines	BS	4/1994	Molecular Biology
Far Eastern University Manila, Philippines	MD	4/1998	Medicine
Chicago Medical School, Chicago, IL	residency	6/2003	Internal Medicine
Wayne State University, Detroit, MI	fellowship	6/2006	Hematology-Oncology

**A. Personal Statement**

I have been actively engaged in clinical and translational research in the field of gastrointestinal cancer with focus in geriatric population and their comorbidities. My research also involves close collaborations with basic researchers other medical disciplines including psychological issues. The major philosophy of my work is that the translational empiric approach in developing new treatments in this disease must be changed to a biology-driven approach. My interests include targeting signaling pathways, immunotherapy and supportive care that involves multidisciplinary approach to cancer care.

**PROFESSIONAL EXPERIENCE**

8/2014 to present Associate Professor in Department of Medicine, Stony Brook University  
Director of Outpatient Oncology

9/2010- 8/2014 Assistant Professor, in Oncology, Karmanos Cancer Institute, NCI-designated Comprehensive Cancer Center and Wayne State University, Detroit, MI

7/2006 to 9/2010, Staff Physician; G. V. Montgomery VA Medical Center Jackson, MS  
Assistant Professor, University of Mississippi, Department of Medicine, Division of Oncology

**MEMBERSHIP**

2010 to 2014 Member/ vice chair of the Phase I Institutional Review Board at Wayne State University  
2006 to 2014 Member of Southwest Oncology Group(SWOG), GI subcommittee  
2003 to present Member of American Society of Clinical Oncology (ASCO)  
2007 to 2010 Member of the Jackson VAMC Institutional Review Board  
2003-2006 served Quality Assurance Committee at Karmanos Cancer Institute/Wayne State University

Board Certification:

Program Director/Principal Investigator (Last, First, Middle):

2007- Board certified in Hematology, American Board of Internal Medicine  
 2006- Board certified in Medical Oncology, American Board of Internal Medicine  
 2003- 2013 Board certified in Internal Medicine, American Board of Internal Medicine

## HONORS/Awards

2012 WSU School of Medicine – College Teaching Award  
 2009 Travel grant from International Society of GI oncology  
 2007 Mississippi Research, “Young Investigator Award”  
 2006 Merit Award form American Society of Clinical Oncology  
 2005 Fellowship travel grant for ASCO  
 1998 cum laude for Doctor of Medicine  
 1998 Most Outstanding Medical Student Award  
 1994 cum laude for BS Molecular Biology  
 1994 Phi Kappa Phi Honor Society

## C. Selected Peer-reviewed Publications

1. Fujiki M, Aucejo F, **Choi M**, Kim R., Neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: where do we stand? *World J Gastroenterol*. 2014 May 14;20(18):5308-19.
2. **Choi M**, Kim R, Saif MW. Is there a role for 2<sup>nd</sup> line chemotherapy in pancreatic cancer? *Journal of Pancreas* 2014 Mar 10;15(2):106-9
3. Yano H, Thakur A., **Choi M**, et. al. Ipilimumab augments antitumor activity of bispecific antibody-armed activated T cells derived from colorectal and pancreatic cancer patients. *Journal of Translational Medicine*, 2014 Jul 9;12:191
4. Al-Hajeli M, Asfar A, **Choi M**. Nab-paclitaxel: potential for the treatment of advanced pancreatic cancer. *Oncotarget and Therapy*, 2014 7:1-6.
5. Salem M, Jain N, Dyson G, **Choi M**, Shields AF, Critchfield J, Philip PA. Radiographic parameters in predicting outcome of patients with hepatocellular carcinoma treated with yttrium-90 microsphere radioembolization. *ISRN Oncology*, 2013 Sep 15;2013:538376. doi: 10.1155/2013/538376;PMID 24167742
6. Kim R, Mahipal A, **Choi M**, Saif MW. Biomarkers for pancreatic cancer: Is it ready for primetime? *Journal of Pancreas*, 2013 Jul 10;14(4):309-11. DOI: 10.6092/1590-8577/1676.
7. Tait L, Meyer J, McSpadden E, Cheng J, Baciewicz F, Meropol N, Cohen S, Wozniak A, **Choi M**, Konski A. Women at increased risk for cardiac toxicity following chemoradiation therapy for esophageal carcinoma. *Practical Radiation Oncology*, Oct 2013, Vol 3, Issue 4, Pages e149-e155.
8. Kim R, Tan A, **Choi M**, El-Rayes B. Geographic Differences in Approach To Advanced Gastric Cancer: Is There A Standard Approach? *Crit Rev Oncol Hematol*. 2013 Jun, 1040-8428(13)101-7.
9. Bang H, Littrup P, Currier B, Goodrich D, **Choi M**, Heilbrun L, Goodman A. Percutaneous Cryoablation of Metastatic Lesions from Colorectal Cancer: Efficacy and Feasibility with Survival and Cost-Effectiveness Observations. *ISRN Minimally Invasive Surgery*. 2012 Sept, Volume 2012, Article ID 942364. DOI: 10.5402/2012/942364.

Program Director/Principal Investigator (Last, First, Middle):

10. **Choi M**, Razzaque S, Kim R. Systemic Therapy of Advanced Pancreatic Cancer: Has the Landscape Changed? Clin Adv Hematol Oncol. 2012 Jul;10(7):442-51. PMID: 23262631
11. Azmi A, Banerjee S, Ali S, Wang Z, Bao B, Beck F, Maitah M, **Choi M**, Shields T, Philip P, Sarkar F, Mohammad R. Network Modeling of MDM2 inhibitor-Oxaliplatin Combination Reveals Biological Synergy in wt-p53 solid tumors. Oncotarget. 2011 May;2(5):378-392.
12. **Choi M**, Craft B, Geraci S. Surveillance and monitoring of adult cancer survivors. American Journal of Medicine. 124(7):598-601, 2011.
13. **Choi M.**, L. Heilbrun, R. Venkatramanamoorthy, Lawhorn-Crews JM, Zalupski MM, Shields AF. Using <sup>18</sup>F Fluorodeoxyglucose Positron Emission Tomography to Monitor Clinical Outcome in Patients Treated with Neoadjuvant Chemo-Radiotherapy for Locally Advanced Pancreatic Cancer. American Journal of Clinical Oncology. 2010 Jun;33(3):257-61.
14. Banerjee S, **Choi M**, Aboukameel Wang Z, Mohammad M, Chen J, Yang D, Sarkar FH, Mohammad RM. Preclinical studies of Apogossypolone, a novel pan inhibitor of Bcl-2 and Mcl-1 synergistically potentiates cytotoxic effect of gemcitabine in pancreatic cancer. Pancreas. 2010 Apr;39(3):323-31.
15. **M. Choi**, P. Jiang, L. Heilbrun, D. Smith, S. Gadgeel. Retrospective review of cancer patients age >80 years old treated with chemotherapy at a comprehensive cancer center. Critical Reviews in Oncology and Hematology. 2008 Sep;67(3):268-72.

#### D. Research Support

Merck (Investigator Initiated), "Prevention of Nausea and Vomiting Secondary to FOLFIRINOX Chemotherapy in GI Cancer Patients", \$62,648 (5/22/12 – present)

Xbiotech USA Inc : 2012-PT023 : 2013-014 : A Pivotal Phase III Study to Evaluate Overall Survival using MABp1 as a Monotherapy in Metastatic Colorectal Cancer Patients with Cachexia, \$ 44,434 (4/9/2013 – 8/2014)

Weill Cornell Medical College : 1208012946 : 2013-035 : An Open-Labeled, Multicenter Phase II Study of Cabazitaxel in Refractory Metastatic Gastric or Gastroesophageal Adenocarcinoma, \$45,000 (7/8/2013-8/2014)

Nordion, Inc., "A Phase III Clinical Trial Evaluating TheraSphere in Patients with Metastatic Colorectal Carcinoma of the Liver who have Failed First Line Chemotherapy", \$40,693 (5/22/12 – 5/21/15)

Nordion, Inc., "A Phase III Clinical Trial of Intra-arterial TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (HCC)", \$27,540 (6/21/12 – 6/20/15)

Myriad Genetics, Inc., "A Prospective, Randomized, Open-Label Trial Comparing OnDose® AUC Optimized 5-FU Based Administration versus Standard Body Surface Area (BSA) Dosing in Metastatic Colorectal Cancer Patients (mCRC) Treated with mFOLFOX6", \$44,467 (7/10/12 – 7/9/13)

Genentech, "A Phase II, Multicenter, Open-Label, Randomized Study Evaluating the Efficacy and Safety of FOLFIRI + MEHD7945A versus FOLFIRI + Cetuximab in Second Line in Patients with KRAS Wild-Type Metastatic Colorectal Cancer", \$189,659 (7/18/12 – 7/1/15)

Program Director/Principal Investigator (Last, First, Middle):

Kyowa Hakko Kirin Pharma, Inc., "Phase I/II Study of KRN330 plus Irinotecan after First-Line or Adjuvant FOLFOX/CapOx Failure in Patients with Metastatic Colorectal Cancer", \$125,152 (4/15/11 – 4/14/14)

Oncothyreon, Inc., "Phase 1/2 Study of PX-866 and Cetuximab", \$ 164,539 (10/11/11 – 10/10/2013)

Abbott Laboratories, "An Open-Label, Randomized Phase 3 Study of the Efficacy and Tolerability of Linifanib (ABT-869) vs Sorafenib in Subjects with Advanced Hepatocellular Carcinoma (HCC) (M10-963)", \$82,150 (2010 – 2011)

KCI, Immunotherapy Treatment of Advanced Colorectal and Pancreatic Cancer with anti-CD3 x anti-Erbitux Armed Activated T Cells (Phase Ib). Role: PI. \$60,000 10/8/11- 8/ 2014

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Styliani-Anna (Stella) E. Tsirka	POSITION TITLE Professor of Pharmacological Sciences		
eRA COMMONS USER NAME (credential, e.g., agency login) stsirka			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Aristotle Univ of Thessaloniki, Greece	BSc	10/84	Chemistry
Aristotle Univ of Thessaloniki, Greece	PhD	01/89	Biochemistry

**A. Personal statement.** My laboratory explores the interactions and communications between the nervous and immune systems in physiological and pathological settings, such as glioma, stroke, epilepsy, multiple sclerosis. Many students and postdocs have worked over the years in these projects. I have been a member of the Molecular and Cellular Pharmacology (MCP/HBH) graduate program since 1998. Between 2003 and 2014 I served as the Director of the MCP/HBH Program. I have trained many graduate students in the Program as dissertation supervisor, and have served in numerous research advisory committees for students. I have mentored four MSTP students and serve on the committees of several others. Since the beginning of 2013 I also put together and direct the Stony Brook University Scholars in BioMedical Sciences program, which is based on the concepts of the HHMI Med-into-Grad programs, facilitating the exposure of graduate students in Life Sciences programs to translational clinical and medical science. I have also mentored several postdoctoral fellows and research scientists who have moved on to successful academic careers. My research has been funded by NIH and other funding sources. I have also been organizing and participating in ethics training for the MCP/HBH graduate students for many years. In addition to having been Graduate Program Director, I serve on the Admissions committee of the program and have participated in the program's recruitment efforts. I am certainly very committed to ensuring that we maintain and enhance the training environment of the MCP/HBH and MSTP programs, we recruit every year a group of smart, dedicated and diverse students, and help them develop into successful scientists in different scientific careers in academia, industry, policy and teaching.

**B. Positions and Honors.****Professional Positions**

1986-1989 Predoctoral Fellowship from IKY (The Greek Foundation of Fellowships)  
 1989- 1992 Postdoc fellow, Microbiology and Immunology, UCSF (Advisor: Dr. P. Coffino)  
 1992 Lecturer, Dept of Biochemistry, University of Athens, Greece  
 1993-1997 Postdoc Res. Associate, Pharmacology, SUNY Stony Brook, N.Y. (Advisor: Dr. S. Strickland)  
 1993 NIH-NIDDKD Postdoctoral Award  
 1994-1995 IHFSPO Postdoctoral Award  
 1998- 2000 Res. Asst. Professor, Dept of Psychiatry, SUNY Stony Brook, NY  
 1998- Member of SUNY Stony Brook IACUC  
 1998-1999 Targeted Research Award, SUNY Stony Brook (Neurological Disease)  
 2002- 2004 Carol M. Baldwin Breast Cancer Research Award  
 2000- 2003 Assistant Professor, Dept of Pharmacological Sciences, SUNY Stony Brook, NY  
 2003- 2014 Director, Molecular and Cellular Pharmacology Graduate Program, SUNY Stony Brook, NY  
 2004- 2008 Associate Professor, Dept of Pharmacological Sciences, SUNY Stony Brook, NY  
 2004 - 2010 Scientific advisory board of National Parkinson Foundation  
 2006- 2010 Established Investigator Award of the American Heart Association (National)  
 2007- 2010 Dean's Leadership Advisory Group

Program Director/Principal Investigator (Last, First, Middle):

- 2007 Dean's award for excellence in service to Graduate Education by a graduate program director
- 2008 - Professor, Dept of Pharmacological Sciences, SUNY Stony Brook, NY
- 2011 - Chair, Stony Brook University IACUC
- 2011 - President, Stony Brook University Hellenic Studies Center
- 2012 - Director of Stony Brook University Scholars in BioMedical Sciences (Med-into-Grad) Program

**Study Sections:** Grant Reviewer for Alzheimer's Association (2002-present); AHA-EIA (2011); NIH/NSC-C (2004); NIH/NST2 (2005-2009); NIH/SRB-M (2006); NIH/BDCN-90L/BINP (2004-2010, 2011); ZHD1 DRG-D (2011); AHA-Brain 1 (2007-); NIH-TWDA (2014-); NSF-GRFP (2014-)

1. S.E. Tsirka, A. Gualandris, D.G. Amaral, S. Strickland (1995) Excitotoxin-induced neuronal degeneration and seizure are mediated by tissue-type plasminogen activator. *Nature* 377:340-344.
2. Y.-P. Wu, C.-J. Siao, W. Lu, T.-C. Sung, M.A. Frohman, P. Milev, T.H. Bugge, J.L. Degen, J.M. Levine, R.U. Margolis, S.E. Tsirka. (2000) The tPA/plasmin extracellular proteolytic system regulates hippocampal mossy fiber reorganization through a novel proteoglycan substrate. *J. Cell Biol.* 148:1295-1304
3. M.M. Siddiq, and S.E. Tsirka. (2004) Tissue plasminogen activator and zinc are reciprocal antagonists of neurotoxicity. *Mol. Cell. Neurosci.* 25:162-171.
4. Emmetsberger J, Mirrione MM, Zhou C, Siddiq M, Fernandez-Monreal M, Ji K, SE Tsirka (2010) Tissue Plasminogen Activator alters intracellular sequestration of zinc through interaction with the transporter ZIP4, *J. Neurosci.* 30(19):6538-47 PMID: PMC2872103
5. Ji K, Akgul G, Wollmuth LP, Tsirka SE. (2013) Microglia actively regulate the number of functional synapses. *PLoS One.* 8(2):e56293.
6. Nissen JC, Selwood D, Tsirka SE (2013) Tuftsin signals through its receptor neuropilin-1 via the transforming growth factor beta pathway. *J Neurochem*, 127(3):394-402.
7. Abraham AB, Bronstein R, Reddy AS, Maletic-Savatic M, Aguirre A, Tsirka SE. (2013) Aberrant Neural Stem Cell Proliferation and Increased Adult Neurogenesis in Mice Lacking Chromatin Protein HMGB2. *PLoS One.* 8(12):e84838.
8. Yao Y, Tsirka SE. (2011) Mouse MCP1 C-terminus inhibits human MCP1-induced chemotaxis and BBB compromise. *J Neurochem.* 118(2):215-23. PMID: PMC3129361

#### **Additional publications relevant to the field**

9. S.E. Tsirka, A.D. Rogove, S. Strickland (1996) Tissue plasminogen activator and neuronal cell death. *Nature* 384:123-124.
10. A.D. Rogove, S.E. Tsirka. (1998) Neurotoxic responses by microglia elicited by excitotoxic injury in the mouse hippocampus. *Curr.Biol.* 8: 19-25.
11. Yao Y and Tsirka SE. Removal of the C-terminal domain of MCP1 by plasmin allows for the formation of a potent chemokine gradient (2010) *J. Biol. Chem*, 285(41):31509-16. PMID: PMC2951225
12. Sierra A, Encinas JM, Deudero JJP, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Tsirka SE, Maletic-Savatic M (2010) Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell*, 7:483-95 NIHMS233563
13. Talos F, Abraham A, Vaseva A, Holembowski L, Tsirka SE, Scheel A, Bode D, Dobbelsstein M, Bruck W, Moll UM (2010) p73 is an Essential Regulator of Neural Stem Cell Maintenance in Embryonal and Adult CNS Neurogenesis. *Cell Death Diff*, 17:1816-29 NIHMS263398
14. Bukhari N, Torres L and Tsirka SE. (2011) Axonal Repair in Spinal Cord Injury via Chondroitinase and the Tissue Plasminogen Activator (tPA)/Plasmin System, *J. Neurosci*, 31(42):14931-43. NIHMS333768.
15. Vaseva, AV, Holzmann, S, Ji, K, Tsirka, SE and Moll, UM (2012) p53 protein regulates the mitochondrial permeability transition pore during oxidative stress-induced necrosis and ischemic stroke. *Cell*, 149(7):1536-48

#### **D. Research Support**

##### Active

Program Director/Principal Investigator (Last, First, Middle):

2014-19 NASA: Remote, In Situ and Synchrotron Studies for Science and Exploration (RIS<sup>4</sup>E) PI: Glotch, (Role: Co-I, \$25K/year)

2014-2017 NIH-IRACDA: postdoctoral fellowship for Jillian Nissen (\$45K/year)

2013-2015: SUNYRF Reach: Pilot grant, effects of minocycline and NAC on microglia. PIs: Bergold, Feltri, Tsirka (\$25K)

2014-2016 "Evaluation of the effectiveness of a specially formulated hydrogel to prevent tissue adhesions after surgical intervention". PI: Tsirka (\$40K/year, Targeted Research Opportunities, SBU)

2014-2017 Institutionally-awarded research funds. PI: Tsirka (\$98K/year, SBU)

#### Completed

2012-2014 AHA predoctoral fellowship for Robert Bronstein

2012-2014 Turner predoctoral dissertation fellowship for Luisa Torres

2013-2014: SUNYRF Reach: Pilot collaborative grant assessing the effects of minocycline and NAC on microglia. PIs: Bergold, Feltri, Tsirka

2007-2013 NIH R01NS42168 Microglial effector pathways, PI: Tsirka

2012-2013 NMSS Modulation of T Cell Responses by Microglia During Experiments Allergic Encephalomyelitis (EAE) PI: Tsirka

2007-2012 NMSS, Center Grant from National Multiple Sclerosis Society, (with CoPIs Drs Levine, Colognato, Maletic-Savatic, and van Nostrand)

#### Pending

NIH R01: Role of Phospholipase D3 in late-onset Alzheimer's Disease. PIs: Frohman, Tsirka, van Nostrand

NIH R21: Modulation of neuronal activity by microglia. PIs: Tsirka, Wollmuth

NIH R01: Neurogenesis after stroke - the role of microglia. PI: Tsirka

#### Non Research / Graduate Training

NIH T32 GM0075186 Training Grant in Pharmacological Sciences (Principal Investigator: Styliani-Anna E. Tsirka)

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Powers, Robert Scott

eRA COMMONS USER NAME (credential, e.g., agency login): powerss

POSITION TITLE: Professor of Pathology and Director of Clinical Cancer Genomics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Carleton College, Minnesota	B.A.	05/1974	Mathematics
Columbia University, New York	Ph.D.	03/1983	Biological Sciences
Cold Spring Harbor Laboratory, New York	Postdoctoral	12/1985	Molecular Biology

**A. Personal Statement**

My role in this proposal will be to serve as a research mentor for the Scholars in BioMedical Sciences in Cancer Health Disparities. As a close colleague of Drs. McCombie and Tuveson at Cold Spring Harbor Laboratory, I believe that I can facilitate future development of translational projects involving both SUNY and CSHL for graduate students seeking further training in translational research.

I have been performing cancer genomics research since 1995. My main focus has been to use genome-wide DNA copy number profiling to identify recurrent amplified driver genes and to perform in vitro and in vivo analysis to validate their functional role in oncogenesis. My discoveries in this area include gene amplification of *PPM1D* and *ACK1* in breast and prostate adenocarcinomas and more recently activation of *FGF19* and *POFUT1* by genomic amplification and overexpression in hepatocellular carcinoma. I have experience in building collaborative research teams and am the PI of a multiple investigator NCI-funded Cancer Target Discovery and Validation Center (<http://ocg.cancer.gov/programs/ctd2>). This center continues to develop and apply methods to discover oncogenic drivers and dependencies based on analysis of human cancer genome data. In addition to copy number alterations in cancer, I have applied genome-wide methods to the study of mutational changes, epigenetic changes, and tumor-stromal interactions.

**B. Positions and Honors****Positions and Employment**

1974-1976	Computer Programmer, General Electric Co., NY
1977-1982	Graduate Research Assistant, Dept. of Biological Sciences, Columbia University
1982-1985	Postdoctoral Fellow, Cold Spring Harbor Laboratory, NY
1986-1988	Staff Investigator, Cold Spring Harbor Laboratory, NY
1988-1992	Assistant/Associate Professor, Dept. of Biochemistry, Robert Wood Johnson Medical School
1992-1995	Senior Scientist, Onyx Pharmaceuticals, CA
1995-2004	Scientific Director, Amplicon/Tularik Genomics Division, NY
1995-2004	Adjunct Associate Professor, Cold Spring Harbor Laboratory, NY
2004- 2014	Director, Human Cancer Genome Center & Associate Professor, CSHL
May 1 2014	Research Professor, Cold Spring Harbor Laboratory
May 1 2014	Professor, Department of Pathology, Stony Brook University, NY
May 1 2014	Director, Cancer Genomics, Cancer Center, Stony Brook University, NY

## **Honors and Professional Memberships**

1982-1985	Postdoctoral Fellowship Award, Leukemia Society of America
1988-1992	Editorial Board, Molecular and Cellular Biology
1989	Basil O'Conner Award
1992	A.C.S. Study Section (Molecular Biology)
2007	NCI Molecular Biology Program Project Study Section
2006-2013	NCI Cancer Genetics Study Section
2010-	Scientific Advisory Board, Hope Funds for Cancer Research
2014-	Chair, NCI Cancer Genetics Study Section

## **C. Contributions to Science**

1. **Identification and characterization of evolutionarily conserved genes in the RAS pathway.** I initiated the yeast *RAS* project as a postdoctoral fellow at Cold Spring Harbor in 1983, and continued these studies as an independent investigator through 1995. Although the downstream biochemical effector of RAS proteins was not conserved (adenyl cyclase in yeast, RAF and others in mammalian cells), the upstream activator CDC25 and the enzymes responsible for protein prenylation were highly conserved. Their discovery and study in yeast contributed to understanding their function in all eukaryotes.
  - a. Powers S, Kataoka T, Fasano O, Goldfarb M, Strathern J, Broach J, Wigler M. (1984) Genes in *S. cerevisiae* encoding proteins with domains homologous to the mammalian ras proteins. *Cell*.**36**:607-12.
  - b. Powers S, Michaelis S, Broek D, Santa Anna S, Field J, Herskowitz I, Wigler M. (1986) RAM, a gene of yeast required for a functional modification of RAS proteins and for production of mating pheromone a-factor. *Cell*.**47**:413-22.
  - c. He B, Chen P, Chen SY, Vancura KL, Michaelis S, Powers S. (1991) RAM2, an essential gene of yeast, and RAM1 encode the two polypeptide components of the farnesyltransferase that prenylates a-factor and Ras proteins. *Proc Natl Acad Sci U S A*.**88**:11373-7.
  - d. Lai CC, Boguski M, Broek D, Powers S. (1993) Influence of guanine nucleotides on complex formation between Ras and CDC25 proteins. *Mol Cell Biol*.**13**:1345-52.
2. **Developed and implemented methods that integrate genomic and functional analysis to identify and validate amplified driver genes in cancer.** In the early 2000s, my lab pioneered the oncogene discovery approach of using genome-wide DNA copy number profiling technologies (e.g. RDA, array CGH) together with mapping amplicon epicenters, expression analysis, and functional tests both in vitro and in vivo for oncogenic activity. Unlike other target discoveries in preclinical cancer research, all of our amplified oncogene discoveries have been independently validated.
  - a. Li J, Yang Y, Peng Y, Austin RJ, van Eyndhoven WG, Nguyen KC, Gabriele T, McCurrach ME, Marks JR, Hoey T, Lowe SW, Powers S. (2002) Oncogenic properties of PPM1D located within a breast cancer amplification epicenter at 17q23. *Nat Genet*.**31**:133-4.
  - b. Pei L, Peng Y, Yang Y, Ling XB, Van Eyndhoven WG, Nguyen KC, Rubin M, Hoey T, Powers S, Li J. (2002) PRC17, a novel oncogene encoding a Rab GTPase-activating protein, is amplified in prostate cancer. *Cancer Res*.**62**:5420-4.
  - c. Mu D, Chen L, Zhang X, See LH, Koch CM, Yen C, Tong JJ, Spiegel L, Nguyen KCQ, Servoss A, Peng Y, Pei L, Marks JR, Lowe SW, Hoey T, Jan LY, McCombie WR, Wigler MH, Powers S (2003) Genomic amplification and oncogenic properties of the KCNK9 potassium channel gene. *Cancer Cell*.**3**:297-302.
  - d. van der Horst EH, Degenhardt YY, Strelow A, Slavin A, Chinn L, Orf J, Rong M, Li S, See LH, Nguyen KQ, Hoey T, Wesche H, Powers S. (2005) Metastatic properties and genomic amplification of the tyrosine kinase gene ACK1. *Proc Natl Acad Sci U S A*.**102**:15901-6. PMID 1276100
3. **Focal copy number alterations contain multiple and interacting driver genes.** The paradigm for over 15 years has been that focal copy number alterations, particularly amplicons, have a single driver gene. Scott Lowe and I were the first to discover that focal amplicons can contain two driver genes (*YAP* and *BIRC2/IAP1*). Subsequently, my lab went on to show that one of the most common lung cancer amplicons at 14q13 contains three driver genes, *NKX2-1*, *NKX2-8*, and *PAX9*. Furthermore, we showed that these

three driver genes act synergistically in oncogenic assays. We also found that *FGF19*, only 50 kb distal to *CCND1*, is a co-driver gene of the 11q13 amplicon in liver cancer, and that these two genes functionally interacted in that *FGF19* controlled *CCND1* expression. It is now well established that most focal amplicons contain multiple driver genes, but the importance of functional interaction of multiple driver genes is still largely unappreciated.

- a. Zender L, Spector MS, Xue W, Flemming P, Cordon-Cardo C, Silke J, Fan ST, Luk JM, Wigler M, Hannon GJ, Mu D, Lucito R, Powers S, Lowe SW. (2006) Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. *Cell*.**125**:1253-67. PMID 3026384
- b. Kendall J, Liu Q, Bakleh A, Krasnitz A, Nguyen KC, Lakshmi B, Gerald WL, Powers S, Mu D. (2007) Oncogenic cooperation and coamplification of developmental transcription factor genes in lung cancer. *Proc Natl Acad Sci U S A*.**104**:16663-8. PMID 2034240
- c. Sawey ET, Chanrion M, Cai C, Wu G, Zhang J, Zender L, Zhao A, Busuttill RW, Yee H, Stein L, French DM, Finn RS, Lowe SW, Powers S. (2011) Identification of a therapeutic strategy targeting amplified *FGF19* in liver cancer by Oncogenomic screening. *Cancer Cell*.**19**:347-58. PMID 3061399

**4. Discovery of a targeted therapeutic strategy for *FGF19*-amplified hepatocellular carcinomas.** My lab discovered that amplification and overexpression in hepatocellular carcinomas of *FGF19*, encoding a secreted peptide that is a hepatocyte-specific mitogen, confers a strong selective Fgf19 signaling dependency. This suggested a targeted therapeutic strategy where hepatocellular carcinomas harboring *FGF19* amplification (approximately 15%) be treated with antibody inhibitors of Fgf19. Although the original anti-Fgf19 monoclonal antibody developed by Genentech that we studied was subsequently found to have unacceptable toxicity, two pharmaceutical companies have since then developed inhibitors of Fgf19's receptor (Fgfr4) that are less toxic and one, based on our study and validation by independent laboratories, is proceeding with clinical trials in HCC using *FGF19* amplification as a selective biomarker.

- a. Sawey ET, Chanrion M, Cai C, Wu G, Zhang J, Zender L, Zhao A, Busuttill RW, Yee H, Stein L, French DM, Finn RS, Lowe SW, Powers S. (2011) Identification of a therapeutic strategy targeting amplified *FGF19* in liver cancer by Oncogenomic screening. *Cancer Cell*.**19**:347-58. PMID 3061399

## Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40132415/?sort=date&direction=ascending>

## D. Research Support

### Ongoing Research Support

U01CA168409 NIH (Powers) Role: PI 05/1/12-04/30/17

Computational and functional approaches to validating cancer genome targets.

Goal: Computationally analyze cancer genome data to guide functional screening of candidate oncogenic drivers and dependencies in model systems.

### Completed Research Support

U01CA168409 NIH (Sander) Role: Co-investigator 05/01/12-04/30/14

Supplement for Computational and Functional Approaches to Validating Cancer Genome Targets.

Goal: Develop Dashboard (Web Interface) to Display CTD2 Data

R01CA124648 NIH (Powers) Role: PI 12/1/06-11/30/12

An integrative approach to cancer gene discovery in hepatocellular carcinoma

Goal: Use comparative genomics of human and mouse liver cancer to discover driver genes.

P01 CA013106 NIH (Hannon) Role: Core Director 02/10/05-12/31/13

CSHL Tumor Virus Grant YR 41 Genome & Proteomics Core D

Goal: Directing the Genome & Proteomics facility of the DNA Tumor Virus grant.

RC2CA148532-02 NIH (Powers) Role: PI 09/29/09-08/31/12

### CSHL Molecular Target Discovery and Development Center

This center uses informatic analysis of TCGA data coupled to functional tests in transplantable mouse models to discover new driver genes that underlie the diversity of genomic alterations found in human cancer.

U01CA105388 NIH (Lowe)

Role: Co-investigator

09/1/09-08/31/14

Identifying driver mutations and tumor dependencies by comparative oncogenomics.

Goal: Use oncogenomic screening in mouse models to discover oncogenes and tumor suppressor genes that drive human cancer development and to use synthetic lethal RNAi screens to discover tumor dependencies.

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Lina M. Obeid</b>	POSITION TITLE <b>Professor</b>		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>obeidl</b>			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Rutgers University, Piscataway, NJ	B.S.	1978	Chemistry
American University Beirut, Lebanon	M.D	1983	Medicine
Duke University, Durham, NC	Residency	1983-1987	Internal Medicine
Duke University, Durham, NC	Fellow	1988-1990	Endocrinology

**NOTE: The Biographical Sketch may not exceed four pages.**

### A. Personal Statement

I have the expertise, leadership and motivation necessary to successfully carry out my role as a mentor on this grant application. I have a broad background in Medicine, biochemistry, cell and molecular biology with specific training and expertise in bioactive sphingolipid metabolism and role in cell regulation. In my medical training I gained significant expertise in pathophysiology of disease. As a postdoctoral fellow, I carried out biochemical and molecular and cellular biology studies on G-protein coupled receptors and protein kinase C. As an Assistant and Associate professor at Duke University, I established my research program to investigate the metabolism and role of bioactive lipid mediators in cell regulation, apoptosis and senescence. For the last decade as a Professor in Medicine, Biochemistry and Molecular Biology, I have consolidated my research program and expanded my studies into the role and regulation of bioactive lipids in disease pathobiology with a focus on inflammation, cancer and aging. As PI on several previous VA and NIH-funded grants, I successfully administered the projects and collaborated with other researchers. As a result of these previous experiences, I am aware of the importance of collaboration and communication in science, and of the value of shared instrumentation.

Moreover, through out my career I have been involved in the clinical training of medical students and residents, as well as, the research training of numerous students (in my laboratory and served on thesis advisory committee), post doctoral fellows, and junior faculty. Most of my trainees are in academic positions ranging from assistant and associate professors, staff scientists, and research fellows. I also have significant experience in teaching both in a didactic and in a non-classroom environment. In addition for over 5 years I was Associate Director of the NIH-funded MUSC Medical Scientist Training Program (MSTP), and for the last 10 years I served as PI on a Center of Biomedical Research Excellence (COBRE) in Lipidomics and Pathobiology. All of this extensive experience in training at multiple academic levels has prepared me to have a leadership role as a mentor on this proposal.

In summary, I have a demonstrated record of successful and productive research projects in an area of high relevance for disease, and my expertise and experience have prepared me to lead research projects and to be a mentor for more junior scientists at all levels.

### B. Positions and Honors

1990 - 1992	Associate, Department of Medicine, Duke University
1990 - 1998	Staff Physician Durham Veterans Affairs Medical Center
1992 - 1996	Assistant Professor, Department of Medicine, Duke University
1994 - 1998	Assistant Professor, Department of Cell Biology, Duke University
1996 - 1998	Associate Professor: Department of Medicine, Duke University
1998 - 2012	Staff Physician Ralph H Johnson Veterans affairs Medical Center
1998 - 2012	Boyle Professor of Medicine, Department of Medicine, Medical University of South Carolina

1998 - 2012 Professor, Department of Biochemistry, Medical University of South Carolina  
 2002 - 2011 Associate Director for Aging Biology, Center of Aging, Medical University of South Carolina  
 2002 - 2011 Associate Director, Medical Scientist Training Program, Medical University of South Carolina  
 2012 - Professor of Medicine, Stony Brook University  
 2012 - Dean for Research, Stony Brook University  
 2012- Staff Physician Northport Veterans Affairs Medical Center

**Honors and Awards:** B.S. with honors 1978; Dean's honor list, School of Medicine 1978-83; Member, Alpha Omega Alpha, Honor Medical Society 1982; M.D. with distinction from American University of Beirut, School of Medicine 1983; Hartford Scholar 1989-90; Henry Christian Memorial Award 1990; Clinical Investigator Award, National Institute of Aging 1992-97; James A. Shannon Director's Award 1994-96; Paul Beeson Physician Faculty Scholar 1995-98; First Award, National Institute of Aging 1995-00; Veterans Affairs Merit Award 2000-present; 2002 Elected to membership of Association of American Physicians; AAAS Fellow (2004). JLR lectureship awardee for the FASEB lysophospholipid meeting, august 2013.

**Study Sections:** Veteran's Administration (Ad hoc reviewer); National Science Foundation Ad hoc reviewer; American Federation of Aging Research (Beeson Program, Scientific Advisory Board, 1999 - 2005); American Federation of Aging Research (AFAR) Research Committee Review board (2003-present); AFAR (Atlanta Affiliate, 2003 - present); National Cancer Institute (NCI)-Special Panel for PPG, 1999 & 2001; National Cancer Institute (NCI) Special Panel for RFA CA00-002, 2000; NIH: Permanent Member of Medical Biochemistry then Physiological Chemistry study sections, 2001 – 2005. NIH:Special Emphasis Panel/Scientific Review Group ZRG1 BCMB-S (02) M 2011. NCI Special Emphasis Panel – Provocative Question B, 2013. RFA RM-11016: Regional Comprehensive Metabolomics Resource Cores ZRG1 BST-F (50) R, 2013.

### C. Selected Peer-reviewed Publications (pubs selected from recent pubs and out of ~200 total)

1. Johnson, K.R., Johnson, K.Y., Crellin, H.G., Ogretmen, B., Boylan, A.M., Harley, R.A., and **Obeid, L.M.** (2005) Immunohistochemical Distribution of Sphingosine Kinase 1 in Normal and Tumor Lung Tissue. *JHC* 53(9): 1159-1166.

2. Taha, T.A., Kitatani, K., El-Alwani, M., Bielawski, J., Hannun, Y.A., and **Obeid, L.M.** (2006) Loss of sphingosine kinase-1 activates the intrinsic pathway of programmed cell death: modulation of sphingolipid levels and the induction of apoptosis. *FASEB* 20(3):482-4.

3. Spassieva, S., Bielawski, J., Anelli, V., and **Obeid, L.M.** (2007) Chapter 12: Combination of C17 Sphingoid Base Homologues and Mass Spectrometry Analysis as a New Approach to Study Sphingolipid Metabolism. In *Methods Enzymology*. Volume 434 Lipidomics and Bioactive Lipids: Lipids and Cell Signaling, Brown, H.A (Ed.) ISBN: 978-0-12-373965-0.

4. Anelli, V., Gault, C.R., Cheng, A.B., and **Obeid, L.M.** (2008) Sphingosine Kinase 1 is Up-regulated During Hypoxia in U87MG Glioma Cells: Role of Hypoxia-inducible Factors 1 and 2. *J Biol Chem*. FEB 8; 283(6): 3365-75. **\*PMCID Not applicable to this publication.**

5. Hannun, Y.A., and **Obeid, L.M.** (2008) Principles of bioactive lipid signaling: lessons from sphingolipids. *Nature Reviews Molecular Cell Biology*. Feb 9; (2):139-50. **\*PMCID Not applicable to this publication.**

6. Hammad, S., Crellin, H., Wu, X., Melton, J., Anelli, V., and **Obeid, L.M.** (2008) Dual and Distinct Roles for Sphingosine Kinase 1 and Sphingosine 1 Phosphate in the Response to Inflammatory Stimuli in RAW Macrophages. *POLM*. Mar; 85(3-4):107-14. **PMCID: PMC2290737**

7. Novgorodov, S.A., Gudiz, T.I., **Obeid, L.M.** (2008). Long-Chain Ceramide Is A Potent Inhibitor of the Mitochondrial Permeability Transition Pore. *J Biol Chem*., Sep 5; 283(36):24707-17. **PMCID: PMC2529003**

8. Snider, A.J., Kawamori, T., Bradshaw, S.G., Orr, K.A., Gilkeson, G., Hannun, Y.A., and **Obeid, L.M.** (2009) A Role For Sphingosine Kinase 1 in Dextran Sulfate Sodium-Induced Colitis. *FASEB* Jan; 23(1):143-52. **PMCID: PMC2626622**

9. Kawamori, T., Kaneshiro, T., Okumura, M., Maalouf, S., Uflacker, A., Bielawski, J., Hannun Y.A., **Obeid L.M.** (2009) Role for sphingosine kinase 1 in colon carcinogenesis. *FASEB* Feb; 23(2):405-14. **PMCID: PMC2630788**

10. Spassieva, S.D., Mullen, T.D., Townsend, D.M., and **Obeid, L.M.** (2009) Disruption of ceramide synthesis by CerS2 down-regulation leads to autophagy and the unfolded protein response. *Biochem. J.* 2009 Sep 3. **PMCID: PMC19728861**

11. Siskind LJ, Mullen TD, Rosales KR, Clarke CJ, Hernandez-Corbacho MJ, Edinger AL, **Obeid LM.** The BCL-2 protein BAK is required for long-chain ceramide generation during apoptosis. *J Biol Chem.* 2010 Feb 18. [Epub ahead of print] PMID: 20172858. **PMCID: PMC2825918.**

12. Heffernan-Stroud LA, **Obeid LM.** p53 and regulation of bioactive sphingolipids. *Adv Enzyme Regul.* 2011;51(1):219-28. **PMCID:PMC3078951**

13. Heffernan-Stroud, L. A., Helke, K.L., Jenkins, R.W., DeCosta, A.M., Hannun, Y.A., and **Obeid, L.M.** (2011) Defining a role for sphingosine kinase 1 in p53-dependent tumors. *Oncogene.* 2012 Mar 1;31(9):1166-75. doi: 10.1038/onc.2011.302. Epub 2011 Jul 18. **PMCID:PMC3278571**

14. Chipuk JE, McStay GP, Bharti A, Kuwana T, Clarke CJ, Siskind LJ, Obeid LM, Green DR. (2012) Sphingolipid metabolism cooperates with BAK and BAX to promote the mitochondrial pathway of apoptosis. *Cell.* 2012 Mar 2;148(5):988-1000. **PMID: 22385963**

15. Snider AJ, Wu BX, Jenkins RW, Sticca JA, Kawamori T, Hannun YA, **Obeid LM.** Loss of neutral ceramidase increases inflammation in a mouse model of inflammatory bowel disease. *Prostaglandins Other Lipid Mediat.* 2012 Dec;99(3-4):124-30. doi: 10.1016/j. prostaglandins 2012.08.003. Epub 2012 Aug 31.

16. Gault CR, Eblen ST, Neumann CA, Hannun YA, **Obeid LM .** Oncogenic K-Ras regulates bioactive sphingolipids in a sphingosine kinase 1-dependent manner. *J Biol Chem.* 2012 Sep 14;287(38):31794-803. **PMCID: PMC3442513**

17. Gandy KA, Canals D, Adada M, Wada M, Roddy P, Snider AJ, Hannun YA, **Obeid LM.** Sphingosine 1-phosphate induces filopodia formation through S1PR2 activation of ERM proteins. *Biochem J.* 2013 Feb 1;449(3):661-72. doi: 10.1042/BJ20120213. PMID: 23106337

18. Orr Gandy KA, Adada M, Canals D, Carroll B, Roddy P, Hannun YA, **Obeid LM.** Epidermal growth factor-induced cellular invasion requires sphingosine-1-phosphate/sphingosine-1-phosphate 2 receptor-mediated ezrin activation. *FASEB J.* 2013 Apr 29.

## D. Research Support

### Ongoing

1) Merit Award (Obeid - PI) 10/1/10 - 09/30/2017

Agency: Veteran's Administration

"Bioactive Sphingolipid enzymes as targets in inflammation"

The long-term goal of this project is to define the role of ceramidases and sphingosine kinase in inflammation and to target these enzymes for novel anti-inflammatory therapy.

2) 9R01GM097741-13A1 (Obeid - PI) 3/1/12-5/31/15

Agency: NIGMS (The competing renewal of this grant scored in the 13th% and is expected to be funded)  
Role and Regulation of Ceramide Synthases in Apoptosis

The aims of this proposal is to dissect the role of the novel family of Ceramide Synthases in regulation of specific and distinct pools of ceramide and their role in apoptosis. Moreover this proposal will dissect the role of Bak in regulation of ceramide metabolism.

3) P01 CA097132-11 (Hannun – PI, Obeid - Project 3 Leader)

09/01/014-08/31/19

Agency: NIH/NCI

Sphingolipids in Cancer Biology and Therapy

The aims of this proposal are to study the role of sphingosine kinase in p53 null and mutant cancer development.

## Completed

1) P20 RR17677 (Obeid - PI) 09/26/02 - 04/1/12

Agency: NIH/NCRR

"COBRE in Lipidomics and Pathobiology"

To develop an interactive Center of Lipidomics and Pathobiology that will promote the growth and excellence of research at MUSC. This involves mentoring 5 junior investigators in their respective projects in the area of lipidomics and pathology, as well as three cores.

2) P30 CA138313-01 (Kraft - PI) 04/1/09-03/31/14

Agency: NIH/NCI

Medical University of South Carolina-Cancer Center Support Grant

Leader of Program Lipid signaling in cancer

Major goal: To support the ongoing research infrastructure, research programs, shared resources, developmental funds, and administration of the Hollings Cancer Center at the Medical University of South Carolina to ensure the development of more effective approaches to cancer prevention, diagnosis, and therapy.

3) IR01-GM-62887 (Obeid - PI) 5/01/01 – 8/31/11

Agency: NIH/NIA

"Sphingosine Phosphate in Inflammation"

The main goals of this proposal were focused on the role of sphingosine kinase 1 and sphingosine phosphate in inflammation.

4) 1R01-AG-16583 (Obeid - PI) 09/01/01-08/31/11

Agency: NIH/NIA

"Mitochondrial Ceramide in Chemotherapy-induced Apoptosis"

The long-term goal of this proposal is to develop ceramides as novel therapeutic approaches to cancer treatment. The sphingolipid ceramide has recently emerged as a key regulator of apoptosis in response to multiple inducers such as chemotherapeutic agents, UV radiation, and tumor necrosis factor alpha.

5) Merit Award (Obeid - PI)

01/1/04 - 12/31/08

Agency: Veteran's Administration

"Regulation of Human Alkaline Ceramidases and Role in Cancer Biology "

Specific aims of this grant are to clone two other human homologues of alkaline phytoCDase and determine their enzymatic function in cells and *in vitro*. To study the biochemical and cellular regulation of the two new putative alkaline CDases. To determine the differential regulation and role of the different alkaline CDases in regulation of apoptosis.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Hussain, M. Mahmood

POSITION TITLE: Professor

eRA COMMONS USER NAME (credential, e.g., agency login): mhussain

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Osmania University, Hyderabad, India	M. Sc.	1978	Biochemistry
University of Hyderabad, India	M. Phil.	1979	Intestinal absorption
Oklahoma State University, USA	Ph.D.	1984	Biochemistry
University of Copenhagen, Denmark	Lic. Med.	1986	Biochemistry

**A. Personal Statement**

I joined the Medical College of Pennsylvania as an Assistant Professor in 1991. Since then, my laboratory has been studying lipid absorption and lipoprotein assembly. My laboratory has developed several methods and models to study chylomicron assembly and secretion. We studied secretion of lipids with chylomicrons and showed that newly synthesized triglycerides are preferentially secreted with chylomicrons. We described mechanisms for the absorption and transport of vitamins A and E. We have shown that there are two pathways (apoB-dependent and -independent) involved in cholesterol absorption. Further, we have documented the importance of MTP, ABCA1, ACAT2, apoA1, and apoAIV in these pathways.

Since MTP is an essential chaperone for the assembly of chylomicrons, we have paid much attention to its role in lipoprotein assembly. We studied protein-protein interactions between apoB and MTP, demonstrated two independent functional domains that carry out lipid transfer and apoB binding activities in MTP, and discovered that binding of MTP to lipid vesicles enhances its binding with apoB. We showed that MTP was evolved as a phospholipid transfer protein and acquired triglyceride transfer activity during a transition from invertebrates to vertebrates. Also, provided molecular and biochemical explanations for some missense mutations found in abetalipoproteinemia subjects. We have developed new assays to measure MTP activity using fluorescent lipids. In addition, we showed that MTP transfers phospholipids onto CD1d. In short, I have a long history and demonstrated expertise to study MTP, lipid absorption, and lipoprotein assembly and secretion.

Recently, we revealed that lipid absorption is regulated by circadian rhythms and disruptions in these rhythms causes hyperlipidemia and enhances atherosclerosis in mice. We have also identified a novel regulator, *Ire1<sup>2</sup>*, of intestinal lipid absorption. We showed that *Ire1<sup>2</sup>* regulates MTP expression in the intestine involving post-transcriptional degradation of mRNA. Moreover, we have identified that microRNA-30c regulates lipoprotein production without causing steatosis. We showed overexpression of miR-30c in the livers of mice reduces plasma lipids and atherosclerosis suggesting that it might be a better agent than MTP inhibitors to reduce plasma lipids.

Over the years, I have published 106 peer-reviewed papers and 38 reviews. I have served as the principal investigator on several NIH and AHA grants over the past 25 years. I have managed research groups consisting of visiting scientists (10), clinical fellows (9), junior faculty (3), postdoctoral fellows (17), graduate students (14, including 6 MD, PhD students), rotating students (21), under graduate students (18), and technicians (7), and have ample experience in hiring, training, safety, budget etc. Moreover, I have

collaborated with several national and international researchers and produced several peer-reviewed publications. Hence, I have demonstrated track-record and experience to lead the proposed project.

### **Positions:**

6/87-9/91 Staff Research Investigator, Gladstone Institute for Cardiovascular Disease, UCSF, CA  
 10/91-6/95 Assistant Professor, Pathology and Biochemistry, the Medical College of Pennsylvania  
 7/95-9/99 Associate Professor, MCP Hahnemann University, Philadelphia, PA  
 10/99-4/02 Associate Professor, SUNY Downstate Medical Center, Brooklyn, NY  
 4/02-present Professor, SUNY Downstate Medical Center, Brooklyn, NY  
 4/03-present President, Chylos, Inc., Woodbury, NY  
 09/13-present Research Scientist, VA New York Harbor Healthcare System, Brooklyn, NY  
 05/14-present Distinguished Professor, State University of New York, NY

**Other Experience and Professional Memberships:** Premium professional silver heart member, AHA, Dallas, TX (2005); Editorial board member, Journal of Lipid Research (2008-present); Co-Editor-in-Chief, Nutrition & Metabolism (London) (2004-2008), Editor-in-Chief, Nutrition & Metabolism (London) 2009-present; Editorial board member, Atherosclerosis, thrombosis, and vascular biology (2009-present);

**Grant review committees:** American Heart Association, Southeastern PA Affiliate (1995-1997); Northeast Consortia Peer Review Study Group 2, AHA (2000-2005); Ad hoc reviewer for the NIH: from 1999 to present; WHO Regional Office for Europe, Copenhagen, Denmark (2000); Member, Endocrinology Merit Review Subcommittee, VA (2004-2010); Vice Chair, NE2 Study Group, AHA (2004); Chairman, Northeast 2 Study Group, AHA (2005); AHA National Center (2007-2009); Medical research council, UK (2011); French national research agency (2012-present); Chair, NIH Study section ZDK1 GRB-N (2013);

**B. Honors:** National Merit Scholarship, Government of India (1976-1978); Danish International Development Fellow, Denmark (1980-1981); Boston University School of Medicine Research Award (1986); Irvine H. Page Award, Council on Arteriosclerosis, Thrombosis, and Vascular Biology, AHA (1998); Leonard N. Horowitz Research Award, AHA, Southeastern Pennsylvania Affiliate (1998); Established Investigator, AHA (1999-2002); Outstanding Achievement Award, International Journal of Oncology, Oncology Reports, International Journal of Molecular Medicine, Crete, Greece (2001); President, New York Lipid and Vascular Biology Research Club (2001-2002); Promising Inventor Award, The Research Foundation, SUNY, Albany, NY (2003); Chancellor's Research Recognition Award, The Research Foundation, State University of New York, Albany, NY (2003); Research administration volunteer research award, AHA, New Haven, CT (2005); Chancellor's award for excellence in scholarship and creative activities, Brooklyn, NY (2005); 2011 ATVB Special Recognition Award in Arteriosclerosis, American Heart Association, National Center

**C. Contribution to Science:** Different topics investigated and representative publications in each area are listed below.

### **Involvement of bone marrow in chylomicron remnant catabolism:**

1. **Hussain MM**, Mahley RW, Boyles JK, Fainaru M, Brecht WJ, and Lindquist P (1989) Chylomicron/chylomicron remnant clearance by liver and bone marrow in rabbits: Factors that modify tissue-specific uptake. **J Biol Chem** 264:9571-9582.
2. Mahley RW, Weisgraber KH, **Hussain MM**, Greenman B, Fisher M, Vogel T, and Gorecki M (1989) Intravenous infusion of apolipoprotein E accelerates clearance of plasma lipoproteins in rabbits. **J Clin Invest** 83:2125-2130.
3. Anderson LJ, Boyles JK, and **Hussain MM** (1989) A rapid method for staining large chylomicrons. **J Lipid Res** 30:1819-1824.
4. **Hussain MM**, Mahley RW, Boyles JK, Lindquist PA, Brecht WJ, and Innerarity TL (1989) Chylomicron metabolism: Chylomicron uptake by bone marrow in different animal species. **J Biol Chem** 264:17931-17938.

### **Role of receptors and proteoglycans in chylomicron remnant clearance:**

1. **Hussain MM**, Maxfield FR, Mas-Oliva J, Tabas I, Ji ZS, Innerarity TL, and Mahley RW (1991) Clearance of chylomicron remnants by low density lipoprotein receptor-related/ $\pm_2$ -macroglobulin receptor. **J Biol Chem**

266:13936-13940.

2. Ji ZS, Brecht WJ, Miranda RD, **Hussain MM**, Innerarity TL, and Mahley RW (1993) Role of heparan sulfate proteoglycans in the binding and uptake of apolipoprotein E-enriched remnant lipoproteins by cultured cells. **J Biol. Chem** 268:10160-10167.
3. **Hussain MM**, Innerarity TL, Brecht WJ and Mahley RW (1995) Chylomicron metabolism in normal, cholesterol-fed and Watanabe heritable hyperlipidemic rabbits: Saturation of the sequestration step of the remnant clearance pathway. **J Biol Chem.** 270:8578-8587.
4. **Hussain MM**, Glodberg IJ, Weisgraber KH, Mahley RW, and Innerarity TL (1997) Uptake of chylomicrons by the liver, but not by the bone marrow, is modulated by lipoprotein lipase activity. **Arterioscl Thromb Vasc Biol** 17:1407-1413.

#### **Assembly and secretion of lipids with chylomicrons:**

1. Luchoomun J, and **Hussain MM** (1999) Assembly and secretion of chylomicrons by differentiated Caco-2 cells: nascent triglycerides and preformed phospholipids are preferentially used for lipoprotein assembly. **J Biol Chem** 274:19565-19572.
2. **Hussain MM**, Kancha RK, Zhou Z, Luchoomun J, Zu H, Bakillah A (1996) Chylomicron assembly and catabolism: role of apolipoproteins and receptors. **Biochim Biophys Acta** 1300:151-170.
3. **Hussain MM** (2000) A proposed model for the assembly of chylomicrons. **Atherosclerosis** 148:1-15
4. **Hussain MM**, Kedees MH, Singh K, Athar H, Jamali NZ (2001) Signposts in the assembly of chylomicrons. **Front Biosci** 6:D320-D331.

#### **Secretion of fat-soluble vitamins with chylomicrons:**

1. Nayak N, Harrison EH, and **Hussain MM** (2001) Retinyl ester secretion by the intestinal cells is a highly specific and regulated process that is dependent on the assembly and secretion of chylomicrons. **J Lipid Res** 42: 272-280.
2. During A, **Hussain M M**, Morel DW, and Harrison EH (2002) Carotenoid uptake and secretion by Caco-2 cells: <sup>2</sup>-carotene isomer selectivity and carotenoids interactions. **J Lipid Res** 43:1086-1095.
3. Anwar K, Kayden HJ, and **Hussain MM** (2006) Transport of vitamin E by differentiated Caco-2 cells. **J Lipid Res** 47:1261-1273. Epub 2006 Mar 28.
4. Anwar K, Iqbal J, and **Hussain MM** (2007) Mechanisms involved in Vitamin E transport by primary enterocytes and in-vivo absorption. **J Lipid Res** 48:2028-2038. Epub 2007 June 20.

#### **ApoB-dependent and apoB-independent pathways of lipid absorption:**

1. Iqbal J, Anwar K and **Hussain MM** (2003) Multiple, independently regulated pathways of cholesterol transport across the intestinal epithelial cells. **J Biol Chem** 278:31610-31620. Epub 2003 May 29.
2. Iqbal J, and **Hussain MM** (2005) Evidence for multiple complementary pathways for efficient cholesterol absorption in mice. **J Lipid Res** 46:1491-1501. Epub 2005 April 16.
3. Iqbal J, Parks, JS, **Hussain MM** (2013) Lipid absorption defects in intestine-specific microsomal triglyceride transfer protein and ATP-binding cassette transporter A1 deficient mice. **J Biol Chem** 288:30432-30444. Epub 2013 Sept 09.
4. Iqbal J, Boutjdir M, Rudel LL, **Hussain MM** (2014) Intestine specific MTP deficiency with global ACAT2 gene ablation lowers acute cholesterol absorption with chylomicrons and high density lipoproteins. **J Lipid Res.** 55:2261-2275. Epub 2014 Jul 16.

#### **Methods to measure apolipoproteins and MTP activity:**

1. Bakillah A, Zhou Z, Luchoomun J, and **Hussain MM** (1997) Measurement of apolipoprotein B in various cell lines: correlation between intracellular levels and rates of secretion. **Lipids** 32:1113-1118.
2. Athar H, Iqbal J, Jiang XC, and **Hussain MM** (2004) A simple, rapid and sensitive fluorescence assay for microsomal triglyceride transfer protein. **J Lipid Res** 45:764-772. Epub 2004 Feb 1.
3. Rava P, Athar H, Johnson C, and **Hussain MM** (2005) Transfer of cholesteryl esters and phospholipids as well as net deposition by microsomal triglyceride transfer protein. **J Lipid Res** 46:1779-1785. Epub 2005 May 16.

#### **Protein-protein interactions between apoB and MTP:**

1. **Hussain MM**, Bakillah A, and Jamil H (1997) Apolipoprotein B binding to microsomal triglyceride transfer protein decreases with increases in length and lipidation: implications in lipoprotein biosynthesis.

**Biochemistry** 36:13060-13067.

2. Bakillah A, Jamil H, and **Hussain M M (1998)** Lysine and arginine residues in the N-terminal 18% of apolipoprotein B are critical for its binding to microsomal triglyceride transfer protein. **Biochemistry** 37:3727-3734.
3. **Hussain MM**, Bakillah A, Nayak N, and Shelness GS (1998) Amino acids 430-570 in apolipoprotein B are critical for its binding to microsomal triglyceride transfer protein. **J Biol Chem** 273:25612-25615.
4. Bakillah A, and **Hussain MM (2001)** Binding of microsomal triglyceride transfer protein to lipids results in increased affinity for apolipoprotein B: Evidence for stable microsomal MTP/lipid complexes. **J Biol Chem** 276:31466-31473. Epub 2001 Jun 26.

#### **Role of MTP's phospholipid transfer activity in lipoprotein assembly and secretion:**

1. Rava P, Ojakian GK, Shelness GS and **Hussain MM (2006)** Phospholipid transfer activity of microsomal triglyceride transfer protein is sufficient for the assembly and secretion of apolipoprotein B lipoproteins. **J Biol Chem** 281:11019-11027. Epub 2006 Feb. 13.
2. Rava P, and **Hussain MM (2007)** Acquisition of triacylglycerol transfer activity by microsomal triglyceride transfer protein during evolution. **Biochemistry**. 46:12263-12274. Epub 2007 Oct 09. PMID: 17924655.
3. Khatun I, Zeissig S, Iqbal J, Wang M, Curiel D, Shelness GS, Blumberg RS, **Hussain MM (2012)** Phospholipid transfer activity of microsomal triglyceride transfer protein produces apolipoprotein B and reduces hepatosteatosis while maintaining low plasma lipids in mice. **Hepatology**, 55:1356-1368. Epub 2012 Mar 20.

#### **Contribution to the role of MTP in CD1D and NKT cells:**

1. Dougan SK, Salas A, Rava P, Agyemang A, Kaser A, Morrison G, Khurana A, Kronenberg M, Johnson C, Exley M, **Hussain MM**, Blumberg RS (2005) Microsomal triglyceride transfer protein: lipidation and control of CD1d on antigen presenting cells. **J Exp Med** 202:529-539. Epub 2005 Aug. 08.
2. Dougan SK, Rava P, **Hussain MM**, Blumberg RS (2007) MTP regulated by an alternate promoter is essential for NKT cell development. **J Exp Med** 204:533-545. Epub 2007 Feb 20.
3. Zeissig S, Murata K, Sweet L, Publicover J, Hu Z, Kaser A, Bosse E, Iqbal J, **Hussain MM**, Balschun K, Rocken C, Arlt A, Gunther R, Hampe J, Schreiber S, Baron JL, Moody DB, Liang TJ, Blumberg RS (2012) Hepatitis B virus-induced lipid alterations contribute to natural killer T cell-dependent protective immunity. **Nat Med** 18:1060-1068. Epub 2012 June 17.

#### **Regulation of chylomicron assembly and intestinal lipid absorption by IRE1<sup>2</sup>:**

1. Iqbal J, Dai K, Seimon T, Jungreis R, Oyadomari M, Kuriakose G, Ron D, Tabas I, and **Hussain MM (2008)** IRE1<sup>2</sup> inhibits chylomicron production by selectively degrading MTP mRNA. **Cell Metabolism** 7:445-455. PMID: 18460335.
2. Dai K, Khatun I, and **Hussain MM (2010)** NR2F1 and Ire1<sup>2</sup> suppress MTP expression and lipoprotein assembly in undifferentiated intestinal epithelia cells. **Arterioscl Thromb Vasc Biol** 30:568-574. PMID: 20007910.
3. Iqbal J, Queiroz J, Li Y, Jiang XC, Ron D, **Hussain MM (2012)** Increased intestinal lipid absorption caused by Ire1<sup>2</sup> deficiency contributes to hyperlipidemia and atherosclerosis in Apolipoprotein E-deficient mice. **Circ Res** 110:1575-1584. Epub 2012 May 3.
4. **Hussain MM**, Leung TM, Zhou L, Abu-Merhi S (2013) Regulating intestinal function to reduce atherogenic lipoproteins. **Clinical Lipidology** 8:481-490.

#### **Circadian regulation of plasma lipids:**

1. Pan X, and **Hussain MM (2007)** Diurnal regulation of microsomal triglyceride transfer protein and plasma lipid levels. **J Biol Chem** 282:24707-24719. Epub 2007 June 15.
2. Pan X, and **Hussain MM (2009)** Clock is important for food and circadian regulation of macronutrient absorption in mice. **J Lipid Res** 50: 1800-1813. Epub 2009 Apr 22. PMID: 19387090.
3. Pan X, Zhang Y, Wang L, and **Hussain MM (2010)** Diurnal regulation of MTP and plasma lipid by Clock is mediated by SHP. **Cell Metabolism**. 12:174-186. Epub 2010 Aug 4. PMID: 20674862
4. Pan X, Jiang XC, **Hussain MM (2013)** Impaired cholesterol metabolism and enhanced atherosclerosis in Clock mutant mice. **Circulation** 128:1758-1769. Epub 2013 Sept 06.

#### **MicroRNAs regulating plasma lipids and lipoproteins:**

1. Soh J, Iqbal J, Queiroz J, Fernandez-Hernando C, **Hussain MM (2013)** MicroRNA-30c reduces hyperlipidemia and atherosclerosis in mice by decreasing lipid synthesis and lipoprotein secretion. **Nat. Med.** 19:892-900. Epub 2013 June 9.
2. Soh J, **Hussain MM (2103)** Supplementary site interactions are critical for the regulation of microsomal triglyceride transfer protein by microRNA-30c. **Nutr Metab (Lond)**. 10:56. Epub 2013 Sept 04.
3. Irani S, **Hussain MM (2015)** Role of microRNA-30c in lipid metabolism, adipogenesis, cardiac remodeling and cancer. **Curr Opin Lipidol** In press.

## **D. Research Support**

### **Ongoing Research Support**

“Avoiding toxicity associated with MTP ablation” The aims are to find ways to avoid toxicities associated with MTP inhibition in mice as well as to recognize mechanisms involved in the toxicity associated with MTP inhibition in mice. NIH/NHLBI 3RO1 HL095924-03; 02-01-2010 to 01-31-2014. There is no overlap with the current application. This grant is in no-cost extension and will not be renewed. PI: M. Mahmood Hussain.

“Circadian regulation of lipid metabolism” The aims are to study the role of Bmal1 in the diurnal and food-entrained regulation of plasma lipids. Agency: NIH/NIDDK, RO1 DK081879-02; 07-01-2011 to 08-31-2015. There is no overlap with the current application. PI: M. Mahmood Hussain.

“Regulation of plasma lipids and atherosclerosis by miR-30c” The aims are to understand how miR-30c modulates hyperlipidemia and atherosclerosis and explain mechanisms involved in reducing plasma lipids by miR-30c. Agency: VA Merit Award BX1728; 04-01-2013 to 06-30-2017. There is no overlap with the current application. PI: M. Mahmood Hussain.

“Exploration of lipid transport proteins as drug targets for the treatment of tuberculosis” The goal of this planning grant is to investigate the function and inhibition of lipid transport mechanisms in Mycobacterium tuberculosis, towards developing more effective anti-TB therapeutics. Agency: Health Now/SUNY Network of Excellence in Health; April 17, 2014 – August 31, 2015. There is no overlap with the current application. P.I. Jessica Seeliger; Co:PI: M. Mahmood Hussain.

“microRNA-30c mimics as potential therapeutic agents to lower plasma lipids & regress atherosclerosis”. The goal of this grant is to find out if miR-30c mimics curtail diet induced hyperlipidemia and atherosclerosis in western diet fed C57Bl6J and *Apoe*<sup>-/-</sup> mice. Agency: Technology Accelerator Fund Class 2014 Fund/Research Foundation of SUNY; September 08, 2014 – February 27, 2015. There is no overlap with the current application. PI: M. Mahmood Hussain.

### **Past Research Support**

“Molecular mechanisms of chylomicron assembly” The aims are to study the secretion of free and esterified cholesterol by enterocytes. Agency NIH/NIDDK, RO1 DK46900. This grant started in Jan 1995 and had been renewed several times. The last funding period was from 8-1-2007 to 7-31-2013.

### **Pending**

None

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Girnun, Geoffrey D.</b>	POSITION TITLE <b>Associate Professor</b>		
eRA COMMONS USER NAME GEOFFREY_GIRNUN			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, medical, dental, and training, and include training if available)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Iowa, Iowa City, IA	BS	1994	Physiology/Exer. Science
University of Iowa, Iowa City, IA	PhD	1999	Free Radical Radiation Bio

### A. Personal Statement

Research in my lab is focused on linking fundamental aspects of metabolism and cancer. My research has focused on metabolic regulators and their role in disease. Currently my lab is focused on metabolic alterations in cancer that are driven by specific oncogenic changes. We are also focused on metabolic links underscoring the increase in colon cancer and GI cancer risk in obese and diabetic patients. In particular, we are also interested in how these metabolic changes can be used as biomarkers and in identifying cancer disparities in minority populations. We focus on metabolic regulators driving cancer by promoting metabolic changes associated with cancer as well as specific oncogenes and tumor suppressor genes and the metabolic pathways they control as a means of driving cancer. In addition, we study how metabolic pathways can drive signaling pathways that promote cancer.

### B. Positions and Honors.

#### Positions and Employment

1994-1999	Ph.D. Student, Department of Free Radical and Radiation Biology, University of Iowa College of Medicine
1999-2003	Post-doctoral Fellow, Cell/Cancer Biology, Harvard Medical School and Dana-Farber Cancer Institute
2003-2007	Instructor in Cell/Cancer Biology, Harvard Medical School and Dana-Farber Cancer Inst.
2007-2013	Assistant Professor of Biochemistry and Molecular Biology, University of Maryland School of Medicine
2013-present	Associate Professor of Pathology, Stony Brook University School of Medicine
2013-present	Director, Program in Cancer Metabolism, Stony Brook Cancer Center

#### Honors and Awards

2006-2007	Madeline Franchi Ovarian Cancer Fund Award
2005-2007	Claudia Adams Barr Foundation Award (Co-PI)
2003-2008	NIH K01 Award
2001-2003	Individual National Research Service Award, NIDDK
2000-2001	National Research Service Award Trainee, NCI
1998-1999	Carver Medical Research Trust Award, University of Iowa College of Medicine.
1996	Radiation Research Society "Young Investigator" Award. The 44th Annual Radiation Research Society Meeting, Chicago, IL
1994-1998	Scotia Pharmaceuticals Ltd. (UK) Predoctoral Fellowship

### PUBLICATIONS:

*Selected peer-reviewed publications (in chronological order):*

# **Most relevant to the current application (From list of 26)**

1. Preuss, M., Girnun, G.D., Darby, C., Khoo, N., and Spector, A.A., Robbins, M.E.C. Role of antioxidant enzyme expression in the selective cytotoxic response of glioma cells to  $\gamma$ -linolenic acid supplementation. **Free Rad. Bio. Med.** 28:1143-1156, 2000. PMID: 10832077.
2. Girnun, G.D., Domann, F.E., Moore, S.A., Robbins, M.E. Identification of a functional peroxisome proliferator-activated receptor response element in the rat catalase promoter. **Mol. Endocrinol.** 16:2793-801, 2002. PMID: 12456800.
3. Girnun, G.D., Smith, W.M., Drori, S., Sarraf, P., Mueller, E., Eng, C., Nambiar, P., Rosenberg, D.W., Bronson, R.T., Edelmann, W., Kucherlapati, R., Gonzalez, F.J., Spiegelman, B.M. APC-dependent suppression of colon carcinogenesis by PPAR $\gamma$ . **Proc Natl Acad Sci USA.** 99:13771-6, 2002. PMCID: PMC129773.
4. Nambiar, P.R., Girnun, G.D., Lillo, N.A., Guda, K., Whiteley, H.E., Rosenberg, D.W. Preliminary analysis of azoxymethane induced colon tumors in inbred mice commonly used as transgenic/knockout progenitors. **Int. J. Oncol.** 22:145-50, 2003. PMID: 12469197.
5. \*Drori, S., \*Girnun, G.D., Mueller, E., Sarraf, P., Tou, L., Szwaya, J. Shivdasani, R., Spiegelman, B.M. Hic-5 regulates an epithelial program mediated by PPAR $\gamma$ . **Genes Dev.** 19:362-375, 2005. \*equal authorship PMCID: PMC546514.
6. Girnun, G.D., Naseri, E., Vafai, S., Qu, L., Szwaya, J., Bronson, R., Alberta, J., Spiegelman, B.M. Synergy between PPAR $\gamma$  ligands and platinum-based drugs in cancer. **Cancer Cell.** 11:395-406, 2007. PMCID: PMC2564847.
7. \*Girnun, G.D. Chen, L., Silvaggi, J., Drapkin, R., Chirieac, L.R., Padera, R.F., Upadhyay, R., Vafai, S.B., Wiessleder, R., Mahmood, U., Naseri, E., Buckley, S., Li, D., Force, J., McNamara, K., Demetri, G., Spiegelman, B.M., \*Wong, K.K. Regression of drug-resistant lung cancer by the combination of rosiglitazone and carboplatin. **Clin. Cancer Res.** 14:6478-6486, 2008. PMCID: PMC2696122. \*Co-corresponding author
8. Girnun, G.D. PPAR $\gamma$ : A new independent marker for colorectal survival. **Gastroenterology.** 136:1157-1160, 2009. PMID: 19236969.
9. Souza, D.R., Pierce, A., Girnun, G., Passaniti, A. Glucose metabolism, transcriptional regulation and angiogenesis. 2009 **Current Topics Biochem. Res.** 11, 41-55.
10. Bhalla, K., Hwang, B.J., Dewi, R., Twaddell, W., Girnun, G.D. The metabolic coactivator PGC1 $\alpha$  promotes tumor growth by coordinating a gene expression program driving de novo fatty acid synthesis. **Cancer Res.** 71:6888-6898, 2011, PMID21914785
11. Bhalla, K, Hwang, B., Dewi, R., Choi, J-H., Dewi, R., Ou, L., Twaddell, W., Mclenithan, J., Voronkov, M., Stock, M., Perez, E., Stock, J., Pozharskiy, E., Girnun, G.D. N-Acetyl Farnesyl Cysteine is a novel class of PPAR $\gamma$  ligand with partial and full agonist activity *in vitro and in vivo*. **J. Biol Chem.** 286: 41626-416335, 2011 PMID: 21979952
12. Bhalla, K, Hwang, B., Dewi, R., Twaddell, W., Girnun, G.D. Metformin prevents hepatocellular carcinoma by antagonizing hepatic lipogenesis. **Cancer Prev Res.** 5: 544-552, 2012, PMID:22467080
13. Girnun, G.D. The diverse role of the PPAR $\gamma$  Coactivator-1 family of transcriptional coactivators. **Seminars in Cell and Developmental Biology. Cancer Cell Metabolism Issue.** 23:381-384, 2012, PMID: 22285815
14. Mehrabian, Z, Clerc, P, Carey, G, Michael Wei, M., Hwang, H., Girnun, G.D., Chen, H., Martin, S.S., Polster, B.M. Rapid detection of a “primed for death” state of BCL-2 dependence in cells using microplate-based respirometry. **PloS One**, 7:e42487, 2012, PMID:22880001
15. Vazquez, F., Lim, J.H., Chin, H., Girnun, G.D., Widlund, H.R., Spiegelman, B.M., Puigserver. The transcriptional coactivator PGC1 $\alpha$  defines a subset of human melanoma tumors with increased mitochondrial capacity and resistance to oxidative stress. **Cancer Cell**, 23:287-301, 2013.
16. Singh, A., Happel, C., Manna, S.K., Acquaaah-Mensah, G., Carratero, J., Kumar, S., Nasipuri, P., Krausz, K.W., Dewi, D, Boros, L.G., Gonzalez, F.J., Gabrielson, E., Wong, K.K., Girnun, G.D.\*, Biswal, S\*. Nrf2 regulates miR-1 and miR-206 to drive tumorigenesis. **J. Clin. Invest.** 123: 2921-2934, 2013. \*Co-corresponding author
17. Choe, C. Chumsri, S., Jones, L., Bhandary, L., Zhao, X.F., Lu, S., Goloubeva, O.G. Polster, B.M., Fiskum, G.M., Girnun, G.D. , Passaniti, A. Control of breast cancer metabolism and differentiation by the RUNX2 oncogene through modulation of SIRT6 suppressor gene expression. **Oncogene, Accepted pending revisions.**

18. Liu, WJ., Bhalla, K., Naseri, E., Hwang, B., Vafai, S., Anders, L., Sicinski, P., Girnun, G.D. Cyclin D1 suppresses gluconeogenesis via inhibition of PGC1alpha. **Diabetes**. 63:3266-78, 2014.

## D. Research Support

### Ongoing Research Support

1R01CA169919-01 Girnun, (PI) 07/09/2012-04/30/2017  
NIH/NCI \$211,248 3 cal

Title: Metabolic control of hepatocellular carcinoma by PGC1alpha

These studies are designed to determine the mechanisms by which PGC1alpha promotes liver cancer. In addition, they designed to determine whether PGC1 is a key mediator explaining increased liver cancer in diabetes.

1R01CA140492-01A1 (Co-I, S. Biswal-PI) 01/01/2010-12/31/2015  
NIH/NCI \$202,700 0.6 cal

Title: Regulation of tumorigenesis and therapeutic resistance by NRF2 in lung cancer. These studies are seeking to define the role of Nrf2 in lung cancer. Dr. Girnuns role is leading these studies in the aspects of metabolism and cancer. No overlap

VA Merit Award (Co-I, Passiniti-PI) 04/13/2013-03/31/2017  
Title: Transcriptional regulation of tumor growth \$263,000 0.6 cal

Start up funds (Girnun, PI)  
Office of the Vice president for Research and Cancer Center

### **Past support**

1R01CA169919-01 Girnun (PI) 09/01/2013-04/30/2014  
NIH/NCI- No cost extension 0.3 cal

Supplement- Collaborative Activities to Promote Metabolomics Research  
Metabolic control of hepatocellular carcinoma by PGC1alpha

KG081400 Girnun (PI) 08/01/08-07/31/2011  
Susan G. Komen Foundation Career Catalyst Development Award

Title: Bioenergetic Control of breast cancer growth by the transcriptional activator PGC1 $\alpha$ . The goal of this project is to determine the role of PGC1 $\alpha$  in breast cancer.

## BIOGRAPHICAL SKETCH

NAME & CONTACT INFORMATION Michael A Frohman 438 CMM 631-632-1476		POSITION TITLE Professor and Chair of Pharmacology Director, Medical Scientist Training Program	
eRA COMMONS USER NAME & E-mail address mfrohman michael.frohman@stonybrook.edu			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
U. of Michigan; Ann Arbor	B.S. High Honors	1978	Chemistry & Cell & Molecular Biology
U. of Pennsylvania; Philadelphia	M.D., PhD.	1985	Medicine. Immunology
U. of Cal. at San Francisco	Postdoc	1986-92	Mammalian Developmental Biology

### A. Personal Statement:

My laboratory cloned the mammalian family of lipid-signaling Phospholipase D genes (PLD1 in 1995, PLD2 in 1997, and MitoPLD in 2006) and has worked on them for the past 18 years while publishing nearly 100 peer-reviewed articles and reviews on PLD and other lipid signaling topics with additional ones in submission. PLD superfamily members are involved in many physiological and pathophysiological settings including immune defenses, cancer, neurodegenerative disease, diabetes, cardiovascular disease, and fertility. Among other approaches, we have recently been generating and publishing findings with mice lacking each of the PLD isoforms, and have uncovered a number of fascinating stories with human health relevance. Recent work has included exploring the potential of using a Phospholipase D small molecule inhibitor as a therapeutic in stroke, Alzheimer's Disease, cardiovascular disease and cancer progression settings.

I have been the Director of the Medical Scientist Training Program (MSTP, MD-PhD) at SBU for 13 years, renewing the T32 training grant three times. I am a graduate myself of an MSTP (U. Penn.), have been continuously funded by NIH for my research since the beginning of my faculty position in 1992, and have trained more than 50 students and fellows, approximately 20% of whom have been URM trainees. I have been an external reviewer of other Graduate and MD-PhD training programs since 2006 and have participated in study section reviews of MSTP T32 training grants and individual F-series NRSAs.

Many of the graduate student trainees in my lab have gone on to excellent research career paths, including URM ones:

Yeku Oladapo (Medgar Evers Coll.), 2006-2010; SBU MSTP (Pharmacology Graduate Program); U. Pitt. Int. Med.; Mt. Sinai Heme-Onc fellowship

Mary Osisami (SBU undergrad), 200—2012; Genetics Graduate Program (current: post-doc, University of Michigan)

Akua Bonsra (SBU undergrad), 2005 – 2010; Pharmacology Graduate Program; Regulatory Affairs Specialist at Technical Resources International, Inc

### B. Positions and Honors

#### Positions:

1992-98; 98-03 Assistant & Associate Professor, Stony Brook University, Dept. Pharmacology  
 1995 – 2003 Director, Medical Pharmacology course, SBU School of Medicine  
 2002 - Director, Molecular Cloning Facility Core, Stony Brook University  
 2003 - Professor, Stony Brook University, Dept. Pharmacology  
 2003 - Director, Medical Scientist Training Program (MD/PhD, MSTP) at Stony Brook University  
 2007 - Chair, Department of Pharmacology

#### Honors and Professional Activities:

1977, 78 Michael Reese, U. Michigan Medical Student Summer Research Scholarship  
 1979-1985 Scholarship: NIH Medical Scientist Training Program

1984	Roy G. William Award
1986, 89	Post-doc Fellowships: American Cancer Society, Leukemia Society Senior Fellowship
1993	Basil O'Connor Young Investigator Award, March of Dimes
1994, 95, 96	NIH Cell Biology 1, HED-2 Study Section Special Reviewer
1998-2003	Editorial Board, Journal of Biological Chemistry
1998, 2000	Co-Chair, FASEB, ASPET Meetings on Phospholipases, PLD (Vermont, Boston)
1999 - 2003	NIH Special Emphasis Panel Study Section Ad-hoc Reviewer (ZRG1 SSS-Y 01)
2001	Chair, FASEB Meeting on Phospholipase D (Colorado)
2002, 2006, 2009	NIH P01 Special Emphasis Reviewer; NIH NRSA study section adhoc review panel
2004- 2007	Editorial Board, Journal of Endocrinology
2006-	External Advisory Board, Penn State Medical Scientist Training Program
2007-2008	Guest Co-Editor, Special issue on Phospholipase D in BBA Lipids
2007-	Editorial Boards, J. Functional Develop & Embryology; Molecular & Cellular Pharmacology
2009	NIH MPP Study Section Ad-hoc Reviewer
2010	External reviewer, Molecular Medicine Graduate Program, Med. Coll. Of Georgia
2010	Platform speaker, GPCR 2010 symposium, Helsinki, Finland
2011	Keynote speaker, National conference for MD-PhD training, Gwangju, South Korea
2012 -	Review Editorial Board of Frontiers in Mitochondrial Research
2012	NIH T32 Study Section Ad-hoc Reviewer for MSTP applications (February and June)
2013 -	Councilor, <i>Association of Medical School Pharmacology Chairs (AMSPC)</i>
2014 -	Editorial Board, " <i>Handbook of Experimental Pharmacology</i> "
2014 -	Advisory board, DO/PhD program, New York Institute of Technology

### C. Selected Peer-reviewed Publications (Selected from 184 total publications); h-index 61

#### Most relevant to the current application

- Choi, S.-Y., Huang, P., Chan, D.C., and Frohman, M.A. (2006) A common signaling lipid requirement for Mfn-mediated mitochondrial fusion and SNARE-regulated exocytosis. ***Nature Cell Biology*** 8:1255-62.
- Zhao, C., Du, G., Skowronek, K., Frohman, M.A., and Bar-Sagi, D. (2007) Phospholipase D2-generated PA couples EGFR stimulation to Ras activation by Sos. ***Nature Cell Biology***, 9:707-12. PMID: 17486115
- Yang, J.-S. et al. (2008) COPI vesicle fission: a role for phosphatidic acid and insight into Golgi maintenance. ***Nature Cell Biology***, 10:1146-53. PMID: 18776900
- Su, W., Yeku, O., Olepu, S., **Genna, A.**, Park, J.-S., Ren, H., Du, G., Gelb, M.H., Morris, A.J., and Frohman, M.A. (2009) FIPI, a PLD pharmacological inhibitor that alters cell spreading and inhibits chemotaxis. ***Molecular Pharmacology*** 75:437-46. PMID: 19064628
- Nishikimi et al. (2009) Sequential Regulation of DOCK2 Dynamics by Two Phospholipids during Neutrophil Chemotaxis. ***Science***, 324:384-7. PMID: 19325080
- Tsukahara et al. (2010) The novel second messenger Cyclic Phosphatidic Acid Negatively Regulates the Nuclear Hormone Receptor PPAR $\gamma$ . ***Molecular Cell***, 39:421-32.
- Elvers, M., Stegner, D., Hagedorn, I., Kleinschnitz, C., Braun, A., Kuijpers, M.E.J., Boesl, M., Chen, Q., Heemskerk, J.W.M., Stoll, G., Frohman, M.A., and Nieswandt, B. (2010) Impaired integrin  $\alpha$ IIb $\beta$ 3 activation and shear-dependent thrombus formation in mice lacking phospholipase D1. ***Science Signaling***, 3:1-10.
- Dall'Armi, C et al. (2010) The Phospholipase D1 Pathway Modulates Macroautophagy. ***Nature Communications***, 1:142-152.
- Huang, H., Gao, Q., Peng, X.X., Choi, S.-Y., **Sarma, K.**, Ren, H., Morris, A.J., and Frohman, M.A. (2011) piRNA-associated germline nuage formation and spermatogenesis require MitoPLD pro-fusogenic mitochondrial-surface lipid signaling. ***Developmental Cell***, 20:376-387.
- Huang, P., Yeku, O., Zong, H., Tsang, P., Su, W., Xu, X., Teng, S., Osisami, M., Kanaho, Y., Pessin, J.E., and Frohman, M.A. (2011) Phosphatidylinositol-4-Phosphate-5-Kinase  $\square$  Deficiency Alters Dynamics of Glucose-Stimulated Insulin Release to Improve Glucohomeostasis and Decrease Obesity in Mice. ***Diabetes***, 60:454-63.

Chen, Q., Hongu, T., Sato, T., Zhang, Y., Ali, W., Cavallo, J.-A., van der Velden, A., Tian, H., Di Paolo, G., Nieswandt, B., Kanaho, Y., and Frohman, M.A. (2012) Key roles for the lipid signaling enzyme PLD1 in the tumor microenvironment during tumor angiogenesis and metastasis. **Science Signaling**, 5:ra79.

- with accompanying Podcast in *Science Signaling*; highlighted in **Nature Cancer Reviews** (2013) and in the *Cancer Discovery Research Watch* by the American Assoc. for Cancer Research (Nov. 15<sup>th</sup>, 2012).

Osisami, M., Ali, W. and Frohman, M.A. A role for Phospholipase D3 in myotube formation. (2012). **PLoS One**, 7(3): e33341.

Stegner, D., Thielmann, I., Kraft, P. Frohman, M.A., Stoll, G., and Nieswandt, B. (2013) Pharmacological inhibition of phospholipase D protects mice from occlusive thrombus formation and ischemic stroke. **Arteriosclerosis, Thrombosis, and Vascular Biology**, 33:2212-7.

Li, S. et al.. (2013) High throughput sequencing analysis of natural regulatory and conventional T cell receptor repertoires during human H1N1 challenge. **Nature Communications**, 4:2333.

Akiyama, M., Hasegawa, H., Hongu, T., Frohman, M.A., Harada, A., Sakagami, H., and Kanaho, Y. (2014) Trans-regulation of oligodendrocyte myelination by neurons through small GTPase Arf6-regulated secretion of fibroblast growth factor-2. **Nature Communications**, 5:4744.

Mallipattu SK, Horne SJ, D'Agati V, Narla G, Liu R, Frohman MA, Dickman K, Chen EY, Ma'ayan A, Bialkowska AB, Ghaleb AM, Nandan MO, Jain MK, Daehn I, Chuang PY, Yang VW, He JC. (2015) Krüppel-like factor 6 regulates mitochondrial function in the kidney. **J. Clinical Investigation**, 125:1347-61.

#### D. RESEARCH SUPPORT

<b>R01</b> (PI, Frohman)	9/2012 - 8/2016
NIH GM100109 MitoPLD and RNA processing on the mitochondrial surface	

<b>R01</b> (PI, Frohman)	9/1/09 - 8/31/18
NIH GM084251	
Lipid-signaling pathways regulating mitochondrial morphology, energetics, and movement	

<b>Carol Baldwin Breast Cancer Award</b>	7/2013 – 6/2015
Inhibition of PLD1 as a therapeutic approach in breast cancer	

#### Mentored funding

NIH <b>NRSA</b> F31 Predoctoral fellowship to Rochelle Nelson	6/1/13 – 5/31/16
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Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Jian Cao	POSITION TITLE		
eRA COMMONS USER NAME (credential, e.g., agency login)	Professor of Medicine		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
School of Medicine, Zhengzhou University, Henan, China	M.D.	07/85	Medicine
Hospital Attached to Zhengzhou University, Henan, China	Intern	07/86	Medicine
Peking Union Medical College, Tsinghua University, Beijing, China	M.S.	07/92	Experimental Pathology
Cancer Institute, Kanazawa University, Kanazawa, Japan	Postdoctoral	05/95	Molecular Biology of Cancer
Stony Brook University, Stony Brook, NY	Postdoctoral	05/98	Cellular Biology of Cancer

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

**A. Personal Statement**

Dr. Cao is a Medical Scientist whose career began shortly after receiving his medical doctoral degree at Zhengzhou University School of Medicine (Henan Medical University), China. His interest in cancer research began during his training in experimental pathology in Peking Union Medical College, Tsinghua University (Chinese Academy of Medical Sciences) in Beijing, China, where he received his Master Degree of Sciences. Dr. Cao's research background was further strengthened in the field of molecular and cellular biology of cancer during his postdoctoral training in the laboratories of Dr. M. Seiki in Japan and Dr. S. Zucker in New York. He was among the first scientists to discover the membrane type 1-matrix metalloproteinase (MT1-MMP) and Cell Migration-inducing Protein (CEMIP) and demonstrated that these cancer metastasis-driving genes are targetable molecules aimed at preventing cancer dissemination. Dr. Cao joined the faculty at Stony Brook University in 1998 as an Assistant Professor, was promoted to Associate Professor in 2008 and then full Professor in 2014. His work at Stony Brook University led to: 1) the demonstration of the role of MT1-MMP in early cancer dissemination; 2) the discovery of an alternative approach targeting specific MMPs; 3) the identification of a novel surrogate marker in cancer cell migration/invasion; and 4) the development of a powerful screening tool for anti-cancer drug discovery using a three-dimensional cell culture system. His current research interests involve studying three broad aspects of cancer metastasis: 1) to better understand the mechanism of cancer invasion and metastasis; 2) to develop novel tools for early cancer diagnosis and prognosis; and 3) to identify inhibitors of cancer dissemination. Dr. Cao's long-term goal is to develop drugs to prevent metastasis.

**B. Positions and Honors****Positions and Employment**

1986-1989	Lecturer in Pathology, School of Medicine, Henan University, Henan, China
1998-2009	Assistant Professor of Medicine, Stony Brook University, Stony Brook, NY
2005-present	Member, Institute of Chemical Biology & Drug Discovery (ICB&DD)/Stony Brook University
2008-present	Member, Molecular & Cellular Biology Graduate Program/Stony Brook University
2008-present	Member, Molecular & Cellular Pharmacology Graduate Program/Stony Brook University
2008-present	Member, Molecular Genetics Graduate Program/Stony Brook University
2008-present	Assistant Professor of Pathology, Stony Brook University, Stony Brook, NY
2009-2014	Associate Professor of Medicine, Stony Brook University, Stony Brook, NY
2011-present	Member, Chemical Biology Training Program/Stony Brook University
2014-present	Professor of Medicine, Stony Brook University, Stony Brook, NY

Program Director/Principal Investigator (Last, First, Middle):

**Other Experience and Professional Memberships**

1996-present	Member, American Association for Cancer Research (AACR)
2005-2006	Komen Breast Cancer Foundation, Tumor Biology and Cell Biology
2006-2007	Komen Breast Cancer Foundation, Postdoctoral Fellowship Committee
2006	The Israel Science Foundation (Ad hoc)
2008-2009	DOD Breast Cancer Research Program (BCRP) IDEA and Synergistic IDEA Awards
2009-2010	DOD Breast Cancer Research Program (BCRP) Concept Award/Pathobiology-1
2010-2011	DOD Breast Cancer Research Program (BCRP) Concept Award/Pathobiology-3
2010	National Science Foundation (NSF), Chemistry of Life Processes (CLP) Program
2011	DOD Breast Cancer Research Program (BCRP) Postdoctoral Fellowship Award
2012	DOD Prostate Cancer Research Program (PCRP) Idea Development Award, Pathobiology-2
2012	DOD Prostate Cancer Research Program (PCRP) Idea Development Award, Pathobiology-1(Ad hoc)
2012	DMP Study Section, NIH
2012	VA Oncology Merit Review Panel
2013	DMP Study Section, NIH
2013	Breast Cancer Training-PBY peer review panel
2013	The Israel Science Foundation (Ad hoc)
2013	Carol M. Baldwin Breast Cancer Foundation
2012	VA Oncology Merit Review Panel
2013	DOD Prostate Cancer Research Program (PCRP)-Cell Biology-1
2013	2014 State University of New York Collaboration Fund Panel-3 Chemistry
2014	DOD Breast Cancer Training-PBY peer review panel
2014	NIH Director's Early Independence Award peer review panel
2014	DOD Breast Cancer Research Program_ Breakthrough Award peer review panel
2014	DMP Study Section, NIH
2014	VA Oncology Merit Review Panel
2015	DOD Breast Cancer Research Program_ Breakthrough Award peer review panel
2012-present	Academic Editor: PLoS ONE, The Public Library of Science
2012-present	Member, Editorial Board: Journal of Cancer Research & Therapy, NobleResearch Publisher
2012-present	Managing Editor, Frontiers in Bioscience
2012-present	Member, Editorial Board: Dataset Papers in Biology, Hindawi Publishing Corporation
2012-present	Member, Editorial Board: International Journal of Chronic Diseases, Hindawi Publishing Corporation
2013-present	Member, Editorial Advisory Board, Current Cancer Drug Targets, Bentham Science Publishers
2006-2008	Member, Subcommittee on Animal Studies (IACUC) of VA Hospital, Northport, NY
2008-present	Serve as an interviewer for recruiting graduate students for MCB, Genetics, Pharmacology, and Medical Scientist Training Program (M.D./Ph.D.), Stony Brook University
2008-present	Member/co-chair, The Admissions Committee for the Molecular and Cell Biology and Genetics Programs/Stony Brook University
2009-2010	Member of Undergraduate Council of the University Senate, Stony Brook University
2012-present	Executive Core Oversight Committee, School of Medicine, Stony Brook University
2012-2015	Central Microscopy Imaging Center Core Advisory Committee, School of Medicine, Stony Brook University
2012-present	Member of Graduate and Research Committee, University Faculty Senate of the State University of New York (SUNY System)
2012-present	Member of the Department of Medicine's Research Committee, Stony Brook University

**Honors:**

1982-1986	Scholarship to School of Medicine, Zhengzhou University, Henan, China
1982-1986	Distinguished Graduate Student Award, School of Medicine, Zhengzhou University, Henan, China
1993-1994	Research Fellowship award, Ministry of Education, Science, and Culture of Japan
1997-1998	Research Fellowship award, American Heart Association
1998	AACR-Bristol-Myers Squibb Young Investigator Award, New Orleans, LA

Program Director/Principal Investigator (Last, First, Middle):

1998-2001 Postdoctoral Traineeship award, US Army Medical Research and Materiel Command  
 2001 American Association for Cancer Research Scholar-in-Training Award, New Orleans, LA  
 2001 Gordon Research Conference-Matrix Metalloproteinases travel award, Italy  
 2001-2004 Scientist Development Grant award, the American Heart Association  
 2001-2004 New Investigator Award by US Army Medical Research and Materiel Command (PCRP01)  
 2002 American Association for Cancer Research, Scholars in Cancer Research, San Francisco, CA  
 2014 Basic Science Award, Dept. Of Medicine, Stony Brook University

**C. Selected Peer-reviewed Publications (Selected from 55 peer-reviewed publications)**Most relevant to the current application

1. **Cao J**, Kozarekar P, Pavlake M, Chiarelli C, Bahou WF, Zucker S. (2004). Distinct roles for the catalytic and hemopexin domains of membrane type 1-matrix metalloproteinase metalloproteinase in substrate degradation and cell migration. **J Biol Chem**. 279(14):14129-39. PMID: 14729674
2. **J. Cao**, M. Hymowitz, C. Conner, W. Bahou and S. Zucker (2000). The propeptide domain of membrane type 1-matrix metalloproteinase acts as an intramolecular chaperon when expressed in trans with the mature sequence in COS-1 cells. **J.Biol.Chem.**, Vol.275:29648-29653, PMID:10889191
3. **Cao J**, Chiarelli C, Kozarekar P, and Adler HL. (2005). MT1-MMP Promotes Human Prostate Cancer Invasion and Metastasis. **Thromb Haemost**. 93:770-8, PMID: 15841326
4. **Cao J**, Rehemtulla A, Pavlaki M, Kozarekar P, Chiarelli C. (2005). Furin directly cleaves proMMP-2 in the trans-Golgi network resulting in a non-functioning proteinase. **J Biol Chem**. 280:10974-80. PMID: 15637056
5. **Cao J**, Chiarelli C, Richman O, Zarrabi K, Kozarekar P, Zucker S. (2008). MT1-MMP induces epithelial-to-mesenchymal transition (EMT) in prostate cancer. **J Biol Chem**. 283(10):6232-40. PMID: 18174174
6. Antoine Dufour, Nicole Sampson, Stanley Zucker and **Jian Cao** (2008). Role of the Hemopexin Domain of Matrix Metalloproteinases in Cell Migration, **J Cell Physiol**. 217(3):643-51. PMID: 18636552
7. Dufour A, Zucker S, Sampson NS, Kuscus C, **Cao J**. (2010). Role of matrix metalloproteinase-9 (MMP-9) dimers in cell migration: design of inhibitory peptides\* **J. Biol. Chem.**, 12;285(46):35944-56. PMID: 20837483 \* This work was featured in F1000Prime, Post-publication Peer Review, Jan. 2011
8. Antoine Dufour, Nicole S. Sampson, Jian Li, Cem Kuscus, Robert Rizzo, Jennifer L. DeLeon, Jizu Zhi, Nadia Jaber, Eric Liu, Stanley Zucker and **Jian Cao** (2011). Small Molecule Anti-Cancer Compounds Selectively Target the Hemopexin Domain of Matrix Metalloproteinase-9 (MMP-9)\*, **Cancer Res**. 71(14):4977-88. PMID:21646471  
 \* This work was featured in **SciBX** (JUNE 23, 2011 • VOLUME 4 / NUMBER 25), a publishing collaboration between **BioCentury** Publications, Inc. and **Nature** Publishing Group.
9. Kevin Zarrabi, Antoine Dufour, Jian Li, Cem Kuscus, Jizu Zhi, Youjun Hu, Nicole S. Sampson, Stanley Zucker, and **Jian Cao** (2011). Inhibition of matrix metalloproteinase-14 (MMP-14)-mediated cancer cell migration\* **J. Biol. Chem**. 286(38):33167-77. PMID:21795678  
 \* This work was featured in F1000Prime, Post-publication Peer Review, Aug. 2011
10. Nguyen HL, Zucker S, Zarrabi K, Kadam P, Schmidt C, **Cao J** (2011). Oxidative stress and prostate cancer progression are elicited by membrane-type 1 matrix metalloproteinase. **Mol Cancer Res**. 9(10):1305-18. PMID: 21849471
11. Li J, Zucker S, Pulkoski-Gross A, Kuscus C, Karaayvaz M, Ju J, Yao H, Song E, **Cao J**. (2012) Conversion of Stationary to Invasive Tumor Initiating Cells (TICs): Role of Hypoxia in Membrane Type 1-Matrix Metalloproteinase (MT1-MMP) Trafficking. **PLoS One** 7(6):e38403; PMID:22679501.  
 \* This work was featured in Faculty of 1000, Post-publication Peer Review, June 2012
12. Cem Kuscus, Nikki Evensen, Deborah Kim, You-Jun Hu, Stanley Zucker, and **Jian Cao** (2012):Transcriptional and Epigenetic Regulation of KIAA1199 Gene Expression In Human Breast Cancer \*. **PLoS One** 2012;7(9):e44661, PMID 22970280.  
 \* This work was featured in World Biomedical [ISSN: 2328-0166]
13. Nikki A Evensen, Cem Kuscus, Kevin Zarrabi, Antoine Dufour, Pournima Kadam, You-jun Hu, Ashleigh Pulkoski-Gross, Hoang-Lan Nguyen, Wadie F. Bahou, Stanley Zucker, and **Jian Cao** (2013) Unraveling the Role of KIAA1199, A Novel Endoplasmic Reticulum Protein in Cancer Cell Migration, **J Natl Cancer Inst**. 105(18):1402-16. PMID: 23990668
14. Nikki A. Evensen, Jian Li, Jie Yang, Xiaojun Yu, Nicole S. Sampson, Stanley Zucker, and **Jian Cao** (2013)

Program Director/Principal Investigator (Last, First, Middle):

Development of a High-Throughput Three-Dimensional Invasion Assay for Anti-Cancer Drug Discovery, **PLoS One** December 2013; 8 (12):e82811. PMID: 24349367

15. Pulkoski-Gross AE, Li J, Zheng C, Li Y, Ouyang N, Rigas B, Zucker S, **Cao J** Repurposing the Anti-psychotic Trifluoperazine as an Anti-metastasis Agent. **Mol Pharmacol**. 2014 Dec 31. PMID: 25552486 [Epub ahead of print]

#### D. Research Support

##### Ongoing Research Support

1R01CA166936-01 (NIH/NCI) Cao (PI) 04/02/2012- 03/30/2017

Title: Integrating Anti-invasive and Anti-growth Therapies Targeting Cancer Metastasis

The major goals of this proposal are to understand the interplay between tumor initiating cells (TICs) and their microenvironment during the transition to invasion and metastasis, as well as to develop a novel treatment reagent to specifically induce invasive TIC death in a preclinical setting.

##### Completed Research Projects for the Past Three Years

\* Carol M. Baldwin Breast Cancer Research Award Cao (PI) 08/01/12-07/31/14

Title: A Novel 3-Dimensional High-Throughput Assay for Targeting Invasive Breast Cancer Cells

The goal of this proposal is to develop a phenotypic screening assay that monitors breast cancer cell invasion in a 3-D environment.

\* R01 CA113553-05 (NCI/NIH) Cao (PI) 04/01/2006- 03/31/2012

Title: Targeting the PEX Domain of MT1-MMP: Novel Cancer Therapy

The major goals of this proposal are to examine the role of MT1-MMP in early stage of cancer invasion and develop specific inhibitors against the hemopexin (PEX) domain of MT1-MMP.

\* R01 CA113553-04S1 (NCI/NIH), Cao (PI, Mentor) 08/01/07- 03/31/11

Title: Targeting the PEX Domain of MT1-MMP: Novel Cancer Therapy This supplemental grant supports Dr. Nguyen's Postdoctoral Traineeship under the PI's R01 grant.

\* Centocor, Inc. Collaborative Award Cao (PI) 09/01/05–12/31/10

The purpose of this award is to improve academic-industry collaboration for evaluation the effect of Centocor's Extracellular Matrix Metalloproteinase Inducer (EMMPRIN) antibody on an orthotopic breast cancer animal model.

\* DOD BCRP Concept Award (W81XWH1010415) Cao (PI) 09/01/10 - 10/31/12

Title: Development of a Novel Cell-Based, High-Throughput Screening Assay for Anti- metastatic Breast Cancer Stem Cell Drug Discovery

The primary goal of this pilot study is to develop a novel cell-based high throughput screening (HTS) assay which allows for the simultaneous determination of metastatic breast cancer stem cell (CSC) migratory ability as well as proteolytic activity.

\* DOD BCRP Concept Award (W81XWH0910358) Shi and Cao (PIs) 09/01/09 - 10/31/11

Title: Detection of Circulating Cancer Cells Using Nano Acoustic Waves

The aim of this proposal is to detect circulating tumor cells (CTCs) in blood of patients with breast cancer using nano acoustic wave (NAW) technology. This is a joint effort between Stony Brook University and Stevens Institute of Technology (NJ).

\* Carol M. Baldwin Breast Cancer Research Award Cao (PI) 11/01/09-10/31/11

Title: Targeting Metastatic Breast Cancer Stem Cell Invasion

The goal of this application is to identify specific inhibitory hits targeting breast cancer stem cells with invasive properties by screening the compound libraries using our 3D invasion HTS assay.

\* Organomed Corporation. Collaborative Award Cao (PI) 06/18/10–12/31/11

Title: Evaluation of Novel Synthetic Compounds Targeting Cancer Cell Proliferation

The purpose of this award is to improve academic-industry collaboration for evaluation the effect of newly generated synthetic compounds inducing cancer cell apoptosis. The compounds are being examined using in vitro and in vivo cancer models.

\* Stony Brook University-Brookhaven National Lab Seed Grant Cao, Sampson, and Fowler (PIs) 09/01/10-08/31/11

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Scharer, Orlando D.</b>	POSITION TITLE Professor of Pharmacological Sciences and Chemistry		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>OSHARER</b>			

EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
ETH, Zürich, Switzerland	Diplom	1991	Chemistry
Harvard University, Cambridge, MA	PhD	1996	Chemistry
Erasmus University, Rotterdam, Netherlands	Postdoc	1996-99	Genetics/Biochemistry

### A. PERSONAL STATEMENT

Research in my laboratory combines organic chemistry, biochemistry and molecular and cellular biology to study the mechanism of mammalian nucleotide excision repair (NER) and interstrand crosslink (ICL) repair. We are interested in two fundamental questions: 1) What are the molecular mechanisms by which DNA repair pathways counteract carcinogenesis and 2) How might we exploit our understanding of DNA repair pathways to improve cancer chemotherapy. Our laboratory has extensive experience in the synthesis of site-specific DNA adducts, including interstrand crosslinks (ICLs) formed by cisplatin, nitrogen mustards and chloro ethyl nitroso ureas as well as adducts formed by environmental mutagens such as AAF. We have used such substrates extensively for the study of the NER and ICL repair pathways. Our studies of the NER pathway have yielded a new model of how the activity of the two endonucleases ERCC1-XPF and XPG are regulated and coordinated to ensure smooth progression through the NER pathway. Our studies of ERCC1-XPF have furthermore provided a molecular bases for how mutations in this heterodimer can lead to three genetic disorders: xeroderma pigmentosum, Fanconi anemia and the progeria XFE syndrome. Our studies using our synthetic ICLs have shown how these lesions interact with translesion synthesis polymerases and yielded important insights into the mechanisms of replication-dependent and -independent ICLs. To date I have trained 18 graduate students and 4 postdocs and numerous undergraduates and rotation students in my laboratory.

### B. POSITION AND HONORS

#### Positions and Employment

1999-2005 Group Leader, START Fellow at the Institute of Molecular Cancer Research, University of Zürich, Switzerland.

2002-2005 Lecturer, Department of Chemistry, ETH Zurich, Switzerland

2005-2011 Associate Professor (with tenure) of Pharmacological Sciences and Chemistry, Stony Brook University, NY

2005- Member, Institute of Chemical Biology and Drug Discovery, Stony Brook University, NY

2005- Member, Molecular and Cellular Biology and Biochemistry and Biophysics Graduate Programs, Stony Brook University, NY

2011- Professor of Pharmacological Sciences and Chemistry, Stony Brook University, NY

#### Awards

1996-1997 Post doctoral fellow of the Swiss National Science Foundation

1997-1999 Human Frontier Science Program long-term postdoctoral fellow

1997 Awarded EMBO postdoctoral fellowship

1999-2005 START fellow of the Swiss National Science Foundation

2001 EMBO Young Investigator Award

2005 NYSTAR Faculty Development Award

## **Selected Professional activities**

2015	Chair, Mammalian DNA Repair Gordon Research Conference
2013	Vice Chair, Mammalian DNA Repair Gordon Research Conference
2013-	Contributing member; <i>Faculty of 1000</i>
2012-	Editorial Board, Environ Mol Mutagen
2011	Guest Editor for special issue of DNA Repair on Nucleotide Excision Repair
2014	NIH CE study section, chair
2012-2013	NIH CE study section, co-chair
2009-2014	NIH CE study section, regular member
2008-2009	NIH CE study section, Ad hoc member
2008	NCI Molecular Oncology P01 SEP member
2001-	External Reviewer for NSF, HFSP, ERC, EMBO, AICR, Cancer Research UK, Wellcome Trust, Research Fondation, Research Cooperation, A*STAR, Swiss Cancer League
2000-	Ad hoc reviewer for >40 Journals, including Science, Nature, Nat Cell Biol, Nat Struct Mol Biol, Nat Chem Biol, Cell, Mol Cell, Genes Dev, EMBO J, PNAS, PLoS Biology, MCB, Angew Chem, JOC, Org Lett.

## **C. SELECT RECENT PEER-REVIEWED PUBLICATIONS** (from a total of 71, h-index = 32)

1. Mukherjee S, Guainazzi A, **Schärer OD** (2014) Synthesis of structurally diverse DNA interstrand crosslinks using postsynthetic reductive amination. **Nucleic Acids Res**, 42, 7429-7435 PMCID: PMC4066762.
2. Hodskinson MR, Silhan J, Crossan GP, Garaycochea JI, Mukherjee S, **Schärer OD**, Patel KJ (2014) Mouse Slx4 is a tumour suppressor that stimulates the activity of the nuclease Xpf-Ercc1 in DNA crosslink repair. **Mol Cell**, 54, 472-484. PMCID: PMC4017094.
3. Guillemette S, Branagan A, Peng M, Dhruva A, **Schärer OD**, Cantor SB (2014) FANCD1 localization by mismatch repair is vital to maintain genomic integrity after UV irradiation. **Cancer Res**, 74, 932-944. PMCID: in progress.
4. Bogliolo M, Schuster B, Stoepker C, Derkunt B, Su Y, Raams A, Trujillo JP, Minguillón J, Ramírez MJ, Pujol R, Casado JA, Baños R, Rio P, Knies K, Zúñiga S, Benítez J, Bueren JA, Jaspers NGJ, **Schärer OD**, Winter JP, Schindler D, Surrallés J (2013) Mutations in ERCC4, encoding the DNA-repair endonuclease XPF, cause Fanconi anemia. **Am J Hum Genet**, 92, 800-806. PMCID: PMC3644630.
5. Su Y, Orelli B, Madireddy A, Niedernhofer LJ, **Schärer OD** (2012) Multiple domains of ERCC1-XPF contribute to DNA binding in nucleotide excision repair **J Biol Chem**, 287, 21846-21855. PMCID: PMC3381147.
6. Enoiu M, Jiricny J, **Schärer OD** (2012) Repair of cisplatin-induced DNA interstrand crosslinks by a replication-independent pathway involving transcription-coupled repair and translesion polymerases. **Nucl Acids Res**, 40, 8593-8964. PMCID: PMC3467066.
7. Enoiu M, Ho TV, Long DT, Walter JC, **Schärer OD** (2012) Construction of plasmids containing site-specific DNA interstrand crosslinks for biochemical and cell biological studies. **Methods Mol Biol** 920, 203-219.
8. Yeo J-E, Khoo A, Fagbemi AF, **Schärer OD** (2012) The efficiencies of damage recognition and excision correlate with duplex destabilization induced by acetylaminofluorene adducts in human nucleotide excision repair. **Chem Res Tox**, 25, 2462-2468. PMCID: PMC3502718.
9. Hentschel S, Alzeer J, Angelov T, **Schärer OD**, Luedtke NW (2012) Synthesis of DNA interstrand crosslinks using a photocaged nucleobase. **Angew Chem**, 51, 3466-3469. Policy Exempt - Not resulting from NIH funding.
10. Fu YV, Yardimci H, Long DT, Ho TV, Guainazzi A, Bermudez VP, Hurwitz J, van Oijen A, **Schärer OD**, Walter JC (2011) Selective bypass of a lagging strand roadblock by the eukaryotic replicative DNA helicase. **Cell** 146, 931-941. PMCID: PMC3209622.
11. Ho TV, Guainazzi A, Derkunt SB, Enoiu M, **Schärer OD** (2011) Structure-dependent translesion synthesis of major groove DNA interstrand crosslinks. **Nucl Acids Res** 39, 7455-7464. PMCID: PMC3177197.

12. Guainazzi A, Campbell AJ, Angelov T, Simmerling C, **Schärer OD** (2010) Synthesis and molecular modeling of a nitrogen mustard DNA interstrand crosslink. **Chem Eur J** 16, 12100-12103.
13. Orelli B, McClendon BT, Tsodikov, OV, Ellenberger T, Niedernhofer LJ, **Schärer OD** (2010) The interaction between ERCC1 and XPA is required for nucleotide excision repair, but not other DNA repair pathways. **J Biol Chem** 285, 3705-3712.
14. Ahmad A, Enzlin JH, Wijgers N, Raams A, Appeldoorn E, Theil AE, Hoeijmakers JHJ, Vermeulen V, Jaspers NGJ, **Schärer OD\***, Niedernhofer LJ\* (2010) Aberrant sub-cellular localization of DNA repair protein XPF: the molecular basis for extracutaneous symptoms in xeroderma pigmentosum. **PLoS Genet** 6, e1000871. PMID:PMC2832669. \*Co-corresponding authors
15. Knipscheer P, Räsche M, Smorgorzewska A, Enoiu M, Ho TV, **Schärer OD**, Elledge SJ, Walter JC (2009) The Fanconi anemia pathway promotes replication-dependent DNA interstrand crosslink repair. **Science** 326, 1698-701. PMID: PMC2909596.

## D. RESEARCH SUPPORT

### Ongoing Research Support

R01CA165911-01      Schärer, OD (PI)      07/01/12-04/30/17

NIH/NCI

Synthesis, structure and repair of DNA interstrand crosslinks.

Role: PI

The major goals of this project are to synthesize and structurally characterize DNA interstrand crosslinks and to characterize how they are processed in cell extracts and by DNA polymerases.

3P01CA092584-11      Tainer, JA (PI)      09/01/11-08/31/16

NIH/NCI

Structural Cell Biology of DNA Repair Machines

Role: Senior Investigator

Structural and biochemical approaches to study the interaction of ERCC1-XPF with XPA, SLX4 and DNA

NN      Begley TJ; Schärer, OD (Co-PIs)      11/01/13-10/31/15

SUNY/RF Research Collaboration Fund (PIs: Begley & Schärer)

Diagnostic Tools for Assessing the Levels and Repair of Cisplatin DNA Adducts in Tumors

Role: Co-PI

Generate antibodies with specificity against various cisplatin-DNA adducts

1R13 CA192553      Schärer, OD (PI)      11/07/14-03/13/15

NIH/NCI/NIA/NIEHS

2015 Mammalian DNA Repair Gordon Research Conference & Gordon Research Seminar

Role: PI

Support for the organization of a Gordon Research Conference and Seminar

### Recently Completed Research Support

P01ES04068      Grollman, A (PI)      07/01/07-08/31/12

NIH/NIEHS

Molecular Toxicology of DNA adducts

Role: Co-Investigator

R01GM080454-01      Schärer, OD (PI)      09/24/07-08/31/11

NIH/NIGMS

Coordination of late steps in the human nucleotide excision repair

R01GM080454-S1      Schärer, OD (PI)      08/14/09-06/31/11

NIH/NIGMS

Coordination of late steps in the human nucleotide excision repair

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Kollmar, Richard	POSITION TITLE Associate Professor, Cell Biology; Assistant Professor and Director of Basic Research, Otolaryngology		
eRA COMMONS USER NAME (credential, e.g., agency login) RKOLLMAR			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Julius-Maximilians-Universität Würzburg, Germany	(Vordiplom)	1983-1985	Chemistry
Ludwigs-Maximilians-Universität München, Germany	Dipl. Chem.	1985-1988	Chemistry
University of Wisconsin–Madison	Ph. D.	1988-1993	Cell and Molecular Biology
University of Texas Southwestern Medical Center	Postdoc	1993-1995	Neuroscience
Rockefeller University	Postdoc	1995-2003	Neuroscience

### A. Personal Statement

I am well suited to join Dr. Martello-Rooney in developing zebrafish into an affordable and high-throughput system to characterize pancreas other GI-derived biopsies from the underserved patient population. First, I have a broad scientific background in several disciplines—graduate training in cell and molecular biology obtained in the McArdle Laboratory for Cancer Research at the University of Wisconsin and postdoctoral training in neuroscience at Southwestern Medical Center and Rockefeller University. Second, I have more than two decades of experience working with zebrafish, starting out with the Neurobiology Course at the Marine Biological Laboratory in Woods Hole, establishing and leading a genetic screen as a postdoc, and continuing to study the molecular genetics of otolith formation in my own laboratory to the present day. We have identified several novel otolith proteins by using proteomics and are investigating their function both in vivo and in vitro. Third, I am leading a scientific collaboration with colleagues in Otolaryngology and in Physiology & Pharmacology to test novel treatments to promote regeneration of the recurrent laryngeal nerve after injury in the rat. This translational project extends a previous collaboration on Wnt signaling and the regeneration of spiral ganglion neurons. Both the otolith and the nerve-regeneration studies have been supported by external funding. Finally, with joint appointments in Cell Biology and Otolaryngology and as the Director of Basic Research for Otolaryngology, I have extensive experience in mentoring research by graduate and medical students, postdoctoral fellows, and residents.

### B. Positions and Honors

#### Positions and Employment

1988-1993	Research Assistant (with Peggy Farnham), McArdle Laboratory for Cancer Research, University of Wisconsin
1993-1995	Research Associate (with A. James Hudspeth), Howard Hughes Medical Institute and Department of Cell Biology and Neuroscience, University of Texas Southwestern Medical Center at Dallas
1995-2003	Research Associate (with A. James Hudspeth), Howard Hughes Medical Institute and Laboratory of Sensory Neuroscience, Rockefeller University, New York
2003-2009	Assistant Professor, Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign
2004-2009	Affiliate, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign
2009-2011	Visiting Associate Professor, Department of Cell Biology, SUNY Downstate Medical Center
2011-present	Assistant Professor, Department of Otolaryngology, SUNY Downstate Medical Center

2011-present Director of Basic and Translational Research, Department of Otolaryngology, SUNY Downstate Medical Center  
 2012-present Associate Professor, Department of Cell Biology, SUNY Downstate Medical Center  
 2013-present Director, Molecular and Cellular Biology Program, School of Graduate Studies, SUNY Downstate Medical Center

#### Other Experiences and Professional Memberships

1993 Neurobiology Course, Marine Biological Laboratory, Woods Hole, MA  
 2002-present Member, Association for Research in Otolaryngology  
 2003-present Member, Society for Neuroscience  
 2013-2015 NIH Special Emphasis Panel/Scientific Review Group on Xenopus Genetics and Genomics  
 2013-present Member, American Academy for Otolaryngology-Head and Neck Surgery

#### **C. Selected Peer-reviewed Publications (Out of 18 total)**

1. **Kollmar R**, Montgomery LG, Fak J, Henry LJ, Hudspeth AJ. Predominance of the  $\alpha 1D$  subunit in L-type voltage-gated  $Ca^{2+}$  channels of hair cells in the chicken's cochlea. *Proc Natl Acad Sci U S A*. 1997 Dec 23;94(26):14883-8. [PMC25132]
2. **Kollmar R**, Fak J, Montgomery LG, Hudspeth AJ. Hair cell-specific splicing of mRNA for the  $\alpha 1D$  subunit of voltage-gated  $Ca^{2+}$  channels in the chicken's cochlea. *Proc Natl Acad Sci U S A*. 1997 Dec 23;94(26):14889-93. [PMC25133]
3. **Kollmar R**. Who does the hair cell's 'do? Rho GTPases and hair-bundle morphogenesis. *Curr Opin Neurobiol*. 1999 Aug;9(4):394-8. Review. [PMID10448167]
4. **Kollmar R**, Nakamura SK, Kappler JA, Hudspeth AJ. Expression and phylogeny of claudins in vertebrate primordia. *Proc Natl Acad Sci U S A*. 2001 Aug 28;98(18):10196-201. [PMC56938]
5. Starr CJ, Kappler JA, Chan DK, **Kollmar R**, Hudspeth AJ. Mutation of the zebrafish choroideremia gene encoding Rab escort protein 1 devastates hair cells. *Proc Natl Acad Sci U S A*. 2004 Feb 24;101(8):2572-7. [PMC356991]
6. Kappler JA, Starr CJ, Chan DK, **Kollmar R**, Hudspeth AJ. A nonsense mutation in the gene encoding a zebrafish myosin VI isoform causes defects in hair-cell mechanotransduction. *Proc Natl Acad Sci U S A*. 2004 Aug 31;101(35):13056-61. [PMC516516]
7. López-Schier H, Starr CJ, Kappler JA, **Kollmar R**, Hudspeth AJ. Directional cell migration establishes the axes of planar polarity in the posterior lateral-line organ of the zebrafish. *Dev Cell*. 2004 Sep;7(3):401-12. [PMID15363414]
8. Asai Y, Chan DK, Starr CJ, Kappler JA, **Kollmar R**, Hudspeth AJ. Mutation of the zebrafish atrophin2 gene disrupts signaling by fibroblast growth factor during development of the inner ear. *Proc Natl Acad Sci U S A*. 2006 Jun 13;103(24):9069-74. [PMC1474007]
9. Vieira M, Christensen BL, Wheeler BC, Feng AS, **Kollmar R**. Survival and stimulation of neurite outgrowth in a serum-free culture of spiral ganglion neurons from adult mice. *Hearing Res*. 230: 17-23, 2007. [PMID17521837; manuscript available at <http://hdl.handle.net/2142/1353>]
10. Kang YJ, Stevenson A, Yau P, **Kollmar R**. Sparc Protein Is Required for Normal Growth and Mineralization of Zebrafish Otoliths. *JARO—Journal of the Association for Research in Otolaryngology* 9: 436-451, 2008. [PMC2580808]
11. Shah SM, Kang YJ, Christensen BL, Feng AS, **Kollmar R**. Expression of Wnt receptors in adult spiral ganglion neurons: Frizzled 9 localization at growth cones of regenerating neurites. *Neuroscience* 164: 478-487, 2009. [PMC2761969; manuscript also available at <http://hdl.handle.net/2142/14823>]
12. Shah SM, Patel CH, Feng AS, **Kollmar R**. Lithium alters the morphology of neurites regenerating from cultured adult spiral ganglion neurons. *Hear Res*. 304: 137-44, 2013. [PMC3773701]
13. Mor N, Naggar I, Das O, Nakase K, Silverman JB, Sundaram K, Stewart M, **Kollmar R**. Quantitative video laryngoscopy to monitor recovery from recurrent-laryngeal-nerve injury in the rat. *Otolaryngol Head Neck Surg*. in press.

#### **D. Research Support**

##### Ongoing Research Support

1 R21 DC013629-01A1 (NIH/NIDCD) Kollmar (PI) 12/1/14-11/30/16  
Restoration of Recurrent-Laryngeal-Nerve Function after Injury in a Rat Model  
This study aims to develop procedures for a reducible injury to the recurrent laryngeal nerve and to test the effect of systemic lithium administration on recovery from unilateral vocal-fold paralysis in rats.  
Role: Principal Investigator

Completed Research Support

2013 AAO-HNSF Percy Memorial Research Award Kollmar (PI) 7/1/13-6/30/14  
Restoration of recurrent-laryngeal-nerve function after injury in a rat model  
This study aims to develop surgical and pharmacological methods to promote nerve regeneration in rats with unilateral vocal-fold paralysis.  
Role: Principal Investigator

1 R01 DC006962-01A1 (NIH/NIDCD) Kollmar (PI) 7/1/05-6/30/13  
Molecular Genetics of Otolith Formation in the Zebrafish  
This study aims to identify the constituent proteins of otoliths and elucidate their role in otolith formation.  
Role: Principal Investigator

National Organization for Hearing Research Kollmar (PI) 2/1/2008-1/31/2009  
Interaction of Wnt-Frizzled- and BDNF-signaling during neurite regeneration from adult spiral ganglion neurons  
The long-term goal of this translationally-oriented project is to improve the fidelity of sound perception with cochlear implants by stimulating the outgrowth of neurites from damaged spiral ganglion neurons.  
Role: Principal Investigator

## BIOGRAPHICAL SKETCH

NAME Shroyer, Kenneth Reed	POSITION TITLE Marvin Kuschner Professor and Chairman Department of Pathology Stony Brook Medicine		
eRA COMMONS USER NAME SHROYER.KEN			
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Colorado College, Colorado Springs, CO	B.A.	1978	Biology
Univ. of CO Graduate School, Denver, CO	Ph.D.	1983	Experimental Pathology
Univ. of CO School of Medicine, Denver, CO	M.D.	1987	Medicine

### A. Personal Statement

Dr. Shroyer is Board Certified in Anatomic and Clinical Pathology (1991), with subspecialty certification in Cytopathology (1995). He is an experienced surgical pathologist and cytopathologist and has also maintained continuous federally-funded grant support since 1993. He was a member of the graduate school at the University of Colorado Health Sciences Center for more than 15 years and has been a member of the Molecular Biology Program at Stony Brook University since 2007. He has trained more than 40 graduate students, medical students, MSTP students, residents, and clinical fellows, many of whom have gone on to complete postdoctoral research fellowships, including some that now hold faculty positions in the United States, Europe and Japan. Dr. Shroyer's research has focused on the molecular characterization of benign, premalignant, and malignant lesions of the female genital tract and a wide range of other anatomic sites. He invented the method of DNP labeling of nucleic acid probes, was a pioneer in the development of methods for *in situ* hybridization of mRNAs in the early 1980s, and was the first to report the analysis of x-chromosome inactivation in archival tissues as a marker of clonality. His laboratory has developed and evaluated the expression of numerous novel molecular assays of cellular immortalization and malignant transformation, including telomerase, HPV, surviving, p16, and B7-H4, using PCR-based methods, immunohistochemistry, and *in situ* hybridization.

### B. Positions and Honors

#### Positions and Employment:

1987-1988	Intern in Anatomic and Clinical Pathology, University of Colorado Health Sciences Center
1988-1991	Resident in Anatomic and Clinical Pathology, Univ. of Colorado Health Sciences Center
1991	Chief Resident in Pathology, University of Colorado Health Sciences Center
1991-1997	Assistant Professor of Pathology, University of Colorado Health Sciences Center
1997-2001	Associate Professor with tenure, University of Colorado Health Sciences Center
2002-2007	Professor with tenure, University of Colorado Health Sciences Center
1991-2007	Graduate Faculty, University of Colorado Health Sciences Center, Graduate School
1993-2007	Director of Cytopathology, University of Colorado Health Sciences Center
2000-2007	Director of Surgical Pathology, University of Colorado Health Sciences Center
2007-present	Marvin Kuschner Professor and Chair, Department of Pathology, Stony Brook University Medical Center, State University of New York
1991-present	Graduate Faculty, Stony Brook University Medical Center, Molecular and Cellular Biology Program

### **Other Experience and Professional Memberships (selected):**

- 2004- Editorial Board, Human Pathology
- 2006- Associate Editor, Journal of Clinical Virology
- 2001- National Cancer Institute Study Section member, including IMAT, Applied Emerging Technologies for Cancer Research, Alliance of Glycobiologists for Detection of Cancer and Cancer Risk, SPOREs in Breast, Cervical, Endometrial, Ovarian, Skin Cancers, Lymphoma, Genitourinary, and Gastrointestinal Cancers and In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- 1991- United States and Canadian Academy of Pathology (Member of the Scientific Advisory Board)
- 1991- American Association for Cancer Research
- 1993- American Society of Cytopathology
- 2002- American Society for Investigative Pathology

### **Honors (selected):**

- 1985-1987 Edgar and Marion Adler Scholar Award, UCHSC
- 1987 Joseph and Regina Glaser Student Research Award, UCHSC
- 1991 Robert H. Fennell, Jr., M.D. Award, Department of Pathology, UCHSC
- Lucien J. Rubinstein Award for the Best Paper on Neuro-oncology. Shared with B.K. Kleinschmidt-DeMasters and M.A. Bitter. The American Association of Neuropathologists

### **Invention (selected):**

Regulation of B7-H4 Expression by miR-34 and its Clinical Utility  
 Stony Brook University Research Foundation Reference Number: R-8128  
 Co-Inventor with Jingfang Ju  
 Disclosure Date: 9/11/2008

### **C. Contribution to Science**

Over the course of my career as a physician/scientist, my research has been focused on the identification and validation of objective molecular approaches to improve diagnostic accuracy in surgical pathology and cytopathology. The ultimate aim of this research has been to provide pathologists with objective molecular markers of cancer that can be integrated and interpreted in the context of tissue histopathology and cytopathology. My initial research focused on the development of methods to define tissue clonality and immortalization, based respectively on the development of methods to define patterns of X-chromosome inactivation in archival microdissected specimens and on the analysis of telomerase expression. These studies contributed to the recognition that epithelial premalignant lesions of the female genital tract are composed of immortalized populations of cells, with key characteristics that overlap with those of invasive carcinoma.

A second major aim has been to identify cancer biomarkers that could be used to improve diagnostic accuracy for premalignant and malignant clinical tissue specimens. My lab pioneered early studies of p16 as a cervical cancer biomarker and was the first to deploy p16 testing as a marker used in Pathology diagnostic laboratories to improve diagnostic accuracy. This work subsequently was expanded to include the analysis of p16, MCMs, and other molecular markers of cervical cancer that could be applied to cervical cytology specimens, with the underlying of improving diagnostic accuracy of the Pap test. Most recently, my lab utilized mass spectrometry of laser capture microdissected tissue specimens and identified keratin 17 (K17) as prognostic biomarker predict patient survival, independent of tumor grade and stage.

## **Research Papers (selected)**

1. Keratin 17 in premalignant and malignant squamous lesions of the cervix: proteomic discovery and immunohistochemical validation as a diagnostic and prognostic biomarker. Escobar-Hoyos LF, Yang J, Zhu J, Cavallo JA, Zhai H, Burke S, Koller A, Chen EI, **Shroyer KR**. Mod Pathol. 2014 Apr;27(4):621-30. Epub 2013 Sep 20. PMID: 24051697
2. Immunohistochemical localization of HE4 in benign, borderline, and malignant lesions of the ovary. Georgakopoulos P, Mehmood S, Akalin A, **Shroyer KR**. Int J Gynecol Pathol. 2012 Nov;31(6):517-23. PMID: 23018214
3. Immunocytochemical colocalization of P16(INK4a) and Ki-67 predicts CIN2/3 and AIS/adenocarcinoma. Singh M, Mockler D, Akalin A, Burke S, Shroyer A, **Shroyer KR**. Cancer Cytopathol. 2012 Feb 25;120(1):26-34. PMID: 22162342
4. B7-H4 overexpression in ovarian tumors. Tringler, B, Liu W, Corral L, Torkko KC, Enomoto T, Davison S. Lucia MS, Heinz DE, Papkoff J, **Shroyer, KR**. Gynecol Oncol. 2006 Jan;100(1):44-52. Epub 2005 Oct 26. PMID: 16256178

## **Complete List of Published Work in MyBibliography:**

<http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/47427615/>

## **D. Research Support**

### **Active**

Department of Veterans Affairs Merit Review (Zucker) 10/01/09-09/30/13, 0.6 months  
Reversibility of Epithelial Mesenchymal Transition in Prostate Cancer.  
Kenneth R. Shroyer, Co-I

Department of Defense. (Sitharaman) 2009-2011  
Tumor-targeting single-wall carbon nanotubes for microwave-based imaging and hyperthermia treatment of breast cancer: A small animal study.  
Kenneth R. Shroyer, Consultant

NIH 1R33CA140084. (Robinson, Shroyer: Subcontract PI) 04/01/11-03/31/15, 0.6 months  
Specific Detection of Cervical Cancers Using Cytometry-Based Molecular Diagnostics.

Coulter Foundation. Pre-clinical Evaluation of Carbon (Balaji Sitharaman) 2011-2013  
Nanostructure-Based High-Performance Contrast Agent for Magnetic Resonance Imaging.  
Kenneth R. Shroyer, Co-I

### **Completed**

Carol M. Baldwin Breast Cancer Research Award (Sitharaman) 11/03/08-11/02/09 0.6 months  
Multifunctional Carbon Nanostructure-Based Platforms for Breast Cancer Theragnostics.  
Kenneth R. Shroyer, Co-I

TRO Program, Proteomics Developmental Projects Award (Shroyer) 2009-2010  
Identifying Biomarkers for Pre-malignant and Invasive Cervical Cancer.  
Kenneth R. Shroyer, PI

TRO Program, Carol M. Baldwin Breast Cancer Research Award (Nemesure) 2009-2010  
Evaluation of a Newly Designed Device for Breast Cancer Screening.  
Kenneth R. Shroyer, Co-I

NIH/NCI 4R33CA110519-02 (Shroyer) 07/01/05-04/30/10 1.80 months  
R33 phased innovation and application award p16 and HPV in low-grade cervical cytologic specimens.  
Kenneth R. Shroyer, PI

Carol M. Baldwin Breast Cancer Research Award (Sitharaman) 11/03/08-11/02/09  
(Targeted Research Opportunities)  
Multifunctional Carbon Nanostructure-Based Platforms for Breast Cancer Theragnostics.  
Kenneth R. Shroyer, Co-I

Proteomics Developmental Projects Award (Kew) 11/03/08-11/02/09, 0.6 months  
Kenneth R. Shroyer, Co-I

Targeted Research Opportunities, Proteomics Developmental Projects Award (Kew) 11/03/08-11/02/09  
Kenneth R. Shroyer, Co-I

RCA125370A (Robinson) 01/01/07-12/31/08  
Specific Biomarkers for Detection of Cervical Cancer Cells Using Flow Cytometry score.  
Kenneth R. Shroyer, Consultant

National Cancer Institute, R21 (Shroyer) 08/01/04-06/30/08  
Phased innovation and application award. p16 and HPV in low-grade cervical cytologic specimens.  
Kenneth R. Shroyer, PI

## RESEARCH &amp; RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator				
Prefix:	First Name*: Ellen	Middle Name	Last Name*: Li	Suffix:
Position/Title*:	Chief			
Organization Name*:	The Research Foundation for SUNY, Stony Brook University			
Department:	Medicine			
Division:	Gastroenterology Hepatology			
Street1*:	101 Nicolls Road-Health Sciences Center			
Street2:	T-17 Room 060			
City*:	Stony Brook			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117948173			
Phone Number*:	631-444-2119	Fax Number:	631-444-8886	E-Mail*: ellen.li@stonybrook.edu
Credential, e.g., agency login: ELLENLI1				
Project Role*: PD/PI		Other Project Role Category:		
Degree Type: MD, PhD		Degree Year: 1980		
		File Name		
Attach Biographical Sketch*:				
Attach Current & Pending Support:				

## PHS 398 Cover Page Supplement

OMB Number: 0925-0001

## 1. Project Director / Principal Investigator (PD/PI)

Prefix:

First Name\*: Ellen

Middle Name:

Last Name\*: Li

Suffix:

## 2. Human Subjects

Clinical Trial? ☒ No ☐ YesAgency-Defined Phase III Clinical Trial?\* ☐ No ☐ Yes

## 3. Permission Statement\*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes ☐ No

## 4. Program Income\*

Is program income anticipated during the periods for which the grant support is requested? ☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount (\$)*	Source(s)*
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

## PHS 398 Cover Page Supplement

## 5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?\* ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: [http://grants.nih.gov/stem\\_cells/registry/current.htm](http://grants.nih.gov/stem_cells/registry/current.htm). Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

## 6. Inventions and Patents (For renewal applications only)

Inventions and Patents\*: ☐ Yes ☒ No

If the answer is "Yes" then please answer the following:

Previously Reported\*: ☐ Yes ☐ No

## 7. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name\*:

Middle Name:

Last Name\*:

Suffix:

☐ Change of Grantee Institution

Name of former institution\*:

## PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	P20Introduction_Overall031915.pdf
2. Specific Aims	P20OverallSpecificAims031915final.pdf
3. Research Strategy*	P20Overall_Research_Strategy031415.pdf
4. Progress Report Publication List	
<b>Human Subjects Sections</b>	
5. Protection of Human Subjects	P2_Protection_of_Human_Subjects_Final.pdf
6. Inclusion of Women and Minorities	P2_IOW_Final.pdf
7. Inclusion of Children	P2_IOC_Final.pdf
<b>Other Research Plan Sections</b>	
8. Vertebrate Animals	Pilot2_VERTEBRATE_ANIMALS_Section_GGM_03-17-15.pdf
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	LOS_Overall.pdf
13. Resource Sharing Plan(s)	Resource_Sharing_Plan_Overall_final.pdf
<b>Appendix (if applicable)</b>	
14. Appendix	

## INTRODUCTION -OVERALL

In this revised planning grant submission entitled “Partnership to Study Racial/Ethnic Differences in GI Cancer Biology” in response to PAR-14-152, we have made many changes in response to the reviewers’ thoughtful comments.

We were pleased that **Pilot Project 1 (P1)**, in which we plan to build an infrastructure to study racial and ethnic differences in colorectal cancer genetics and epigenetics, was rated by the majority of the reviewers as “High Impact”. Since our original submission, **Dr. Jennie Williams** has made significant progress in generating and analyzing high resolution methylation analysis in African American (AA) colon cancer samples. She also acquired 75 AA colon cancer samples through collaborations established last year with **Drs. Salifu and Martello-Rooney**, as they build the biobanking infrastructure for SUNY Downstate.

For **Pilot Project 2 (P2)**, which was rated unanimously as “Moderate Impact”, we have since obtained IRB approval and have successfully grown pancreatic cancer organoids from our first in vivo endoscopic ultrasound guided fine needle core biopsy (EUS-FNB). Generating pancreatic organoids from EUS-FNB provides a means of creating a living biobank of resectable as well as unresectable pancreatic cancers, which represents 80% of all pancreatic cancers. We have prioritized our genetic analysis of the pancreatic organoids to directly address how accurately EUS-FNB derived pancreatic organoids represents potential tumor heterogeneity that is present in the original tumor, by comparing their genome wide copy number variant (CNV) profile with that of parallel surgical resection derived pancreatic organoids. We have also revised the Human Subject Protection section to address reviewer concerns. Reviewers also expressed concerns that the SUNY institutions only serve to provide pancreatic tissues, thus missing opportunities to promote the careers of younger investigators and trainees. In this revised application, **Dr. Gerardo Mackenzie**, who is a young Hispanic NCI funded investigator, has taken the role of SUNY PI for the revised P2. He proposes tumor progression studies in the panel of novel organoid models, to determine whether there are innate cell biological differences between URM and non-URM pancreatic cancer cells. **Dr. Shivakumar Vignesh**, Chief of the Division of Gastroenterology and Hepatology at SUNY Downstate, has also been added as a co-investigator to **P2**. He was recently recruited from the Moffitt Cancer Center in Tampa, Florida where he directed the Advanced Endoscopic Oncology fellowship. As suggested by the reviewers, we have further elaborated on the inclusion of trainees in both pilot projects. We emphasize that the research programs, while clearly at pilot scale, will serve as the platform for SUNY Stony Brook and Downstate, and CSHL to interact on all aspects that would be present in a larger scale program such as sample and data transfer, group communication and decision making and trouble-shooting.

For the revised **Administrative Core**, which was rated unanimously as “Moderate Impact”, **Dr. Joel Saltz** has replaced Dr. Scott Powers, who will no longer be able to devote the effort required. **Dr. Joel Saltz** is founding Chair of the Department of Biomedical Informatics at SUNY Stony Brook, and will assist in planning a platform that will link coded samples with clinical metadata and downstream molecular and histologic data. We have also added **Dr. Yalini**, to coordinate the integration of sample and clinical metadata between the two SUNY campuses and with other campuses in the SUNY system. As the reviewers suggested we have assembled an External Advisory Board.

In the revised pilot Training and Education Program, which was unanimously rated as “Moderate Impact”, **Dr. Patricia Thompson**, recently recruited to the Stony Brook Cancer Center as Associate Director of Basic Research, has joined the leadership for this program. We propose to develop an integrated Scholars in Biomedical Sciences program designed to promote training of Ph.D. trainees from all three institutions in translation science/clinical research where special emphasis will be placed on translating ‘bench-to-bedside’ research into the community practice setting for cancer prevention, diagnosis and treatment. Trainees will work with both a research mentor (SUNY Downstate, Stony Brook or CSHL) and a partnering clinical mentor (SUNY Downstate or Stony Brook). Details on the selection of students, the efficacy of brief training modules, and possible support for participating students (e.g., travel, etc.) are now included. These trainees, along with their research and clinical mentors will be asked to present and/or attend an annual joint Cancer Health Disparities symposium held at the Brooklyn Health Disparity Center (SUNY Downstate) that is sponsored by this planning grant.

## **OVERALL SPECIFIC AIMS**

In this revised planning grant application, we propose to build a collaborative partnership between two SUNY major universities, Stony Brook University and Downstate Medical Center, which serve to both educate and provide health care to communities with cancer health disparities, and the NCI-designated Cancer Center at Cold Spring Harbor Laboratory (CSHL) to study racial/ethnic differences in GI cancer biology. Our institutions have exceptional strengths in computational sciences and in the molecular and cellular biology of cancer (Stony Brook), demonstrated track record of URM graduate and medical education and scientific excellence in health disparities research and education (Downstate) and world-renowned cancer biology and 'omics' technologies at CSHL. This partnership is aimed at addressing the two major target areas: a) cancer research in Specific Aim 1 and b) cancer training, career development and education in Specific Aim 2.

### **Specific Aim 1. Build an integrative partnership between two SUNY medical campuses, Stony Brook and Downstate, and the NCI-designated Cancer Center at Cold Spring Harbor Laboratories to study racial and ethnic differences in GI cancer biology using state of the art technologies.**

A major barrier to investigators studying cancer disparities is lack of access to clinical samples from health disparity populations. To lower this barrier, we will build on the SUNY Stony Brook expertise in molecular and cellular biology of cancer, GI cancer biobanking and bioinformatics, the SUNY Downstate expertise on health disparities research and patient demographics, and the world-renowned cancer biology and 'omics' technologies at CSHL, to plan an integrative platform linking coded patient samples, with rigorously curated longitudinal clinical metadata, and with downstream 'omics and histological imaging data. The collection of deidentified coded samples linked to longitudinal clinical metadata and downstream molecular and histological data will be driven by the two following pilot research programs:

**P1. Genomic comparison of African American and Caucasian colon cancers.** Our goal is to bridge the strengths of the three partnering institutions to fill critical knowledge gaps due to underrepresentation of African Americans in analysis of molecular aberrations at the DNA level from whole genomic sequencing, which will be linked to parallel methylation, RNA, protein and histologic data. We propose to place the expertise to extract critical '-omic' and companion quantitative tissue histology and spatially mapped protein information. With these data, functional and translational studies aimed at discovery of population relevant drug targets, detection biomarkers, and mechanistic understanding of tumors in African American patients in our shared community finally become a reality.

**P2. Pancreatic organoids and personalized chemotherapy for pancreatic cancer.** Recent advances in three-dimensional in vitro propagation of organoids from patient-derived tumors have expanded research opportunities to study the biology of individual patient tumors including characterizing treatment responsiveness. In P2, we aim to optimize this technology to the study of pancreatic ductal organoids derived from minimal procedures to include endoscopic ultrasound guided fine needle core biopsies (EUS FNB). The goal is to establish organoid methods for the purposes of screening novel compounds from minimally derived patient materials. Success in this effort will allow us to access material from surgically unresectable pancreatic cancer patients and to study the impact of disease evolution on treatment. This would expand our research efforts and patient impact by facilitating previously unapproachable characterization of the biology of the ~80% of all pancreatic cancers that present as unresectable. Analyzing organoids obtained from longitudinal samples on pancreatic cancer patients undergoing chemotherapy will guide precise treatment of this disease and facilitate a better understanding of disease heterogeneity among different populations.

### **Specific Aim 2. Build an integrative partnership to promote recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies.**

The integration of faculty, fellows and students from underrepresented and medically underserved communities in the research workforce as well as efforts to enhance awareness of health disparities in the established research workforce are jointly needed to identify, study and solve issues of cancer health disparities. To enhance the research capacities, knowledge and diversity among our cancer research faculty and fellows with research interest in cancer health disparities, we propose to develop a 'Scholars in Biomedical Sciences for Cancer Health Disparities' program for graduate students, particularly those from underrepresented and underserved communities that emphasizes the bench to community cancer care delivery continuum. We will also sponsor an annual Cancer Health Disparities symposium aimed at developing cross-cultural competency in the research workspace including mentorship toward hypothesis based cancer research, and to build awareness of cancer health disparities research findings.

These research and educational programs, while clearly at pilot scale, will serve as the platform for our groups to interact on all aspects that would be present in a larger scale program such as sample and data transfer, group communication and decision making and trouble-shooting.

## OVERALL - RESEARCH STRATEGY

### **1. Overall Objectives**

In this revised planning grant application, we propose to build a collaborative partnership between two SUNY major universities, Stony Brook University and Downstate Medical Center, which serve to both educate and provide health care to communities with cancer health disparities, and the NCI-designated Cancer Center at Cold Spring Harbor Laboratory (CSHL) to study racial/ethnic differences in GI cancer biology.

The overall objectives of this planning grant application are to:

**1A. Build an integrative platform for the three institutions to interact on all aspects of translational GI cancer research that would be present in a larger scale program, such as coordinating sample and data transfer, and to facilitate group communication and decision making and trouble-shooting.** A major barrier to investigators studying cancer health disparities is lack of access to clinical samples and data from health disparity populations. To lower this barrier, we will build on the SUNY Stony Brook expertise in molecular and cellular biology of cancer, GI biobanking and bioinformatics, the SUNY Downstate expertise on health disparities research and patient demographics, and the world-renowned cancer biology and 'omics' technologies at CSHL, to build an integrative platform linking coded patient samples, with rigorously curated longitudinal clinical metadata, and with downstream 'omics and histological imaging data. In this planning grant, we propose to build this platform by focusing on developing consensus on the data elements and common vocabulary, while assembling samples, clinical metadata and downstream 'omics and histological imaging data for pilot projects **P1** and **P2**.

**1B. Promote recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies.** The ability to generalize advances in cancer omics to all patients depends on an understanding of how underlying population differences affect tumor biology, cancer behavior in the clinic and patient factors. Our overall objective is to promote integration of faculty, fellows and students from underrepresented and medically underserved communities in the research workforce, and to enhance awareness of health disparities in the established research workforce. While all three institutions have existing programs aimed at increasing the pool of URM students from cancer health disparity populations in science, technology, engineering and mathematics, we propose to pilot a unique, fully-integrated 'Scholars in Biomedical Sciences for Cancer Health Disparities' program that emphasizes the bench to community cancer care delivery continuum, for graduate students attending any one of the three institutions. A specific objective of this program is to create a high-quality research training environment that facilitates the development of hypothesis-based research to address causes of health disparity whether biological, cultural or economic. There is clearly a need to build mentorship capacity and awareness of cancer health disparities among cancer research faculty at the three institutions. We plan to hold an annual joint Cancer Health Disparities symposium to begin to address these needs. The students, research and clinical mentors in the "Scholars in Biomedical Sciences for Cancer Health Disparities" will be expected to attend and present the results of their work at this annual symposium.

### **2. Existing Resources at SUNY Stony Brook, SUNY Downstate and Cold Spring Harbor Laboratories.**

The existing resources of each of the three partnering institutions, SUNY Stony Brook, SUNY Downstate and Cold Spring Harbor Laboratories are summarized below:

#### **2B SUNY Stony Brook University.**

**1B.1 Provision of care to communities with cancer health disparities by the SUNY Stony Brook University Medical Center.** SUNY Stony Brook Medical Center is Long Island's only academic medical center and is located in Suffolk County, NY. It is the primary provider of medical care to the underserved in Suffolk County. African Americans (AA) constitute 7.4%. Hispanics represents the largest ethnic minority at 17% and this number continues to increase at a rapid pace. Stony Brook investigators have played an active role in reducing racial/ethnic disparities in cancer. SUNY Stony Brook, in collaboration with the county community health care centers, led one of five CDC funded demonstration projects, the Suffolk County Preventive Endoscopy Project (Project SCOPE), to increase colonoscopy screening rates among the underinsured [1,2]. Project SCOPE significantly increased the proportion of Hispanic and AA patients undergoing colonoscopies, even after this program ended [2]. The Stony Brook University Hospital is taking the lead in the Suffolk County Delivery System Reform Incentive Payment (DSRIP) Collaborative. One of the initiatives for Suffolk County DSRIP is to increase

access to high quality chronic disease preventative care and management in both clinical and community settings, including colon cancer screening. Colorectal cancer accounts for 9.9% of all cancer cases and 10.2% of all cancer deaths in Suffolk County. For colorectal screening the focus will be on educational efforts and elimination of barriers to screening for the population over age 50 or those with a family history of colon cancer. Two regions with high colon cancer rates are Brentwood and Central Islip, which are majority minority communities with ~70% Hispanic and ~15% AA individuals.

1B.2 Promoting recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies. SUNY Stony Brook University is one of the 62 research universities that comprise the Association of American Universities (AAU) and is ranked among the top thirty-five public research universities in the US and among the top 1% of universities in the world. It is a top-tier university that educates large numbers of students from low-income families and from diverse backgrounds, especially in high need areas such as science, technology, engineering and mathematics (STEM). Stony Brook University has a substantial minority enrollment and was included in the 2013 Education Trust Report of higher education institutions that are leading in closing the minority college-completion gap.

The Education Opportunity Program (EOP)-Advancement on Individual Merit (AIM) Program at Stony Brook University has played a key role in closing the minority gap. It has been extremely successful and has been featured on the PBS News hour. President Stanley announced allocation of an additional \$1 million to fund the Stony Brook University EOP in 2013. This program admits students who would be 1) ineligible for admission under traditional standards and 2) in need of financial assistance within legislated income guidelines with priority given to applicants from historically disadvantaged backgrounds (e.g. underrepresented minority or URM). Students admitted to the EOP/AIM Academy at Stony Brook University are required to attend a pre-freshman summer academic skills enhancement program that sharpens students' academic skills and prepares them for the rigors of the full-time college enrollment. **Dr. Ellen Li**, the PI of this planning grant application, was instrumental in developing an EOP Chemistry Program, including a prefreshman "head start" chemistry class, tutoring and a freshman seminar aimed at discussing chemistry and biology concepts in the context of the clinical problems of diabetes mellitus and obesity. This program aims to feed students into the highly successful Minority Access to Research Careers (MARC) program at Stony Brook University, directed by **Dr. Jennie Williams**, the SUNY PI for **P1**. This program provides fellowships that support URM undergraduates in their junior and senior years, who seek to pursue doctoral training (PhD or MD/PhD). The fellowship award covers tuition, fees and insurance, an \$11,628/year stipend, opportunity to work in a research laboratory and preparation for the GRE and other costs associated with applying for a PhD or MD/PhD program.

Dr. Vincent Yang, Chairman of the Department of Medicine at Stony Brook University (see Letter of Support), is currently the PI of a multi-institutional American Gastroenterology Association R25 award for short term URM undergraduate students. **Dr. Li** has served as a co-mentor with **Dr. Jennie Williams** for a student from the University of Puerto Rico accepted to this R25 program. Dr. Yang is also co-director of a newly formed Scholars in Biomedical Sciences at SUNY Stony Brook (<http://www.sbms.stonybrook.edu/>). This program engages graduate students in translational research. However, thus far in the two years of its existence no URM graduate student has been accepted to the program which is restricted to SUNY Stony Brook faculty mentors. As described later, we propose in this planning grant to develop a novel integrated Scholars in Biomedicine for Cancer Health Disparities program between the three institutions aimed at training URM PhD graduate students in translational research.

1B.2 Stony Brook Cancer Center and the GI Biobank. Stony Brook University is investing considerable resources in transforming its Cancer Center into a basic and translational hub. This is reflected by the recent new faculty hires, including, Dr. Yusuf Hannun, a world renowned physician scientist in the area of lipid cancer cell signaling, as the new Director of the Stony Brook Cancer Center in 2012. Two of the co-investigators on this planning grant were recently hired, Dr. **Joel Saltz**, founding Chair of the newly formed Department of Biomedical Informatics; and Dr. Patricia Thompson, Associate Director of Basic Research in the Cancer Center. It is also planning the construction of a 250,000-square-foot Medical and Research translation (MART) building that will house 25 cancer biology-oriented labs, and a 30-room cancer clinic. Considerable institutional resources (~ 1 million dollars from philanthropy) have been invested in establishing a GI Biobank, and was founded by **Dr. Li**. The GI BioBank operates as an organ-specific module under the umbrella of the Cancer Center BioBank, directed by Dr. Ken Shroyer, Chair of Pathology (Letter of Support), and operates under the institutional New York State Biobank License issued for SUNY Stony Brook. The collection of specimens in the GI BioBank is organized along the clinical service line engaged in treating colon cancer and pancreatic cancer patients. It thus

represents an interdepartmental effort between the gastroenterologists and surgeons in the Colorectal and Surgical Oncology sections. Specimens are stripped of identifying information and linked by a sample and patient code to rigorously curated longitudinal clinical metadata with defined clinical endpoints. An initial focus of the SUNY Stony Brook GI Biobank was to support **Dr. Jennie Williams**, who is one of few NIH funded URM investigators, but who has been having considerable difficulty identifying and securing the African American colon cancer biospecimens for her research on biological differences between AA and Caucasian colon cancers. The GI Biobank also supported a collaborative pilot project between a URM investigator, **Dr. Denoya**, and **Dr. McCombie**, who directs the DNA Sequencing Shared Resource at the NCI-designated Cancer Center at CSHL to generate epigenetic profiles on clinical samples of colorectal cancers [3]. However as **Dr. Denoya's** project and **Dr. Williams'** project evolved, it became clear that they were seeking to obtain overlapping datasets on overlapping biospecimens. Consequently **P1** represents the integration of two research projects led by two URM investigators requiring overlapping datasets. Since the original submission of this planning grant, two new manuscripts supported by the Stony Brook GI Cancer Biobank have been published by **Dr. Williams** [4,5].

**Dr. Li** initiated monthly GI Cancer Research meetings focused on clinical translational research in 2012. These meetings were attended initially by SUNY Stony Brook clinicians engaged directly in the patient sample collection effort and basic scientists interested in accessing these samples. These meetings fostered the development of new collaborations and new translational projects between clinicians and basic scientists. Since the original submission of this application, the attendance of investigators at SUNY Downstate and CSHL has been facilitated by video conferencing support for these meetings. More recently, the Stony Brook Cancer Center has organized the Long Island Pancreatic Cancer Group, which also served to bringing clinicians and basic scientists together. This meeting was attended by investigators from all three partnering institutions, (see appendix for program). At this meeting, which took place on Jan10, 2014, **Dr. Tuveson's** laboratory presented exciting preliminary results on the feasibility of growing human pancreatic organoids. The interventional endoscopists, including **Dr. Bucobo**, were intrigued about applying this technology to endoscopic ultrasound guided fine needle core biopsies (EUS-FNB). **Dr. Laura Martello-Rooney** had successfully used EUS-FNB to generate pancreatic cell lines but had not tried culturing organoids. This led to the development of **P2** between the three institutions. Since the original submission of this application, unpublished data generated from **P1** and **P2** have been presented and discussed at the monthly GI Cancer Research meetings.

## **2B. SUNY Downstate Medical Center.**

### 2B.1 Provision of care to communities with cancer health disparities by the SUNY Downstate Medical Center.

SUNY Downstate Medical Center is located in a minority, low-income, medically underserved community in Brooklyn, NY. Approximately 75% of the Downstate area residents are of African-American descent and 10% are described as Hispanic-Americans. According to Public Law 106-525 entitled: "Minority Health and Health Disparities Research and Education act of 2000" the Brooklyn communities that Downstate serves fulfill all three criteria for designation as health disparities communities in terms of their 1) density of racial/ethnic minorities, 2) their poverty rates, and 3) because these communities are medically underserved.

### 2B.2 Promoting recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies.

SUNY Downstate Medical Center does not have an undergraduate campus, but is the SUNY-system leader in training minority healthcare professionals, ranking fourth nationally - only behind the 3 Historically Black Medical Colleges - in the number of minority faculty on staff, and has a student body that is 55% minority. SUNY Downstate Medical Center is first among all schools in New York State in the number of URM students. **Dr. Mark Stewart**, Dean of the School of Graduate Studies and Vice Dean of Research at SUNY Downstate, has been at the forefront in improving URM training in STEM and health care.

*2B.2a. Brooklyn Health Disparities Center.* SUNY Downstate Medical Center houses the Brooklyn Health Disparities Center, which is directed by **Dr. Moro Salifu**. The Brooklyn Health Disparities Center is a collaboration of three partners: SUNY Downstate Medical Center (an academic medical center), the Arthur Ashe Institute for Urban Health (an established community based organization) and the Office of the Brooklyn Borough President (a government entity). SUNY Downstate Medical Center is the home of the Brooklyn Health Disparities Center. The Center's mission is to develop and implement models to reduce health disparities in minority and new immigrant populations in Brooklyn through basic, clinical, behavioral and community participatory research, community education and outreach and health professional training.. This Center is currently funded through the NIH P20 under the direction of the Principal Investigator's Drs. **Moro Salifu** (SUNY Downstate Medical Center)

and Ruth Browne (Arthur Ashe Institute for Urban Health). SUNY Downstate Medical Center is one of the nation's leading urban medical centers, located in the East Flatbush section of Brooklyn, one of the country's most ethnically and culturally diverse neighborhoods within a Brooklyn community that has a minority population of over 50%. The Arthur Ashe Institute for Urban Health (AAIUH) is a not-for-profit community-based organization with an extensive background in community-engaged research, intervention design, and leadership in the effort to reduce racial/ethnic health disparities and has extensive networks for recruiting participants into research protocols. The Institute also is located on the SUNY Downstate campus and works in partnership with SUNY Downstate to achieve the goals of the Health Disparities Center. Currently the major projects the Center is focused on are on 1) developing and implementing a community engaged HIV intervention study, and 2) an obstructive sleep apnea community engaged screening project. **Dr. Moro Salifu** plans to expand the scope of the projects supported by the Brooklyn Health Disparities Center through an existing partnership with the Brooklyn chapter of the American Cancer Center and other collaborating community based organizations to facilitate recruitment of URM patients to the proposed studies.

*2B.2b. Existing pipeline programs to increase competitiveness of URM students.* The Early Medical Education Program is operated by Downstate's Office of Minority Affairs. It has run continuously for over 15 years. Each year, a cohort of about 20 under-represented minority students from area colleges are selected. Academic criteria include B level work in college and full participation in 3 summers at Downstate. Successful completion of the program guarantees a place in the College of Medicine. **Dr. Mark Stewart** has taught in this program essentially from the beginning and finds that about ¼ of students are stars by any standards and this program was an enabler for their success. These students compete on their own strengths for the top residencies. About ½ are successful, but average. The program's support was really the difference for these students. Without it, the vast majority of this segment would not have given medical school a chance. These students are consistently excellent physicians because of their life experience and genuine understanding of the struggles our patients contend with. The bottom ¼ simply have too much in the way of outside responsibilities to be able to dedicate the necessary time to be successful. We lose these students along the way to dropping out or dismissal.

*2B.2c. STEM mentoring program.* SUNY Downstate has partnered with the New York Academy of Sciences to serve elementary school students in Brooklyn for over 5 years, with **Dr. Stewart** as the site director. Downstate graduate students have delivered science and math content in various programs. In 2012, the whole of SUNY and the New York Academy of Sciences received National Science Foundation funding to offer a focused program of mentoring in middle schools in cities throughout New York State (the initial 3 were Brooklyn, Utica, and Albany). In our third full academic year of this program, nearly 50 graduate student mentors have been trained.

Downstate has had a longer history of high school engagement, with programs in partnership with the Arthur Ashe Institute for Urban Health, the Society for Neuroscience (The Brooklyn chapter is based at Downstate), and numerous area high schools looking to get students research experiences for the Intel science competitions.

*2B.2d. SUNY Downstate President's Health Disparities Research Fund.* The President's Health Disparities Research fund was been established in 2014 to maximize the diverse biomedical and population-based research strengths across the Downstate campus and facilitate partnerships of our clinical, basic, and public health faculty with industry and the community with the central goal of becoming a major innovator in and focal point for health disparities research. The scope of the Health Disparities Research Fund encompasses transdisciplinary collaboratives in three areas at the outset: 1) Foster basic, translational, clinical, and population-based research programs and partnerships that will target the medical and social priorities of our patient-base, create new knowledge, and accelerate improvements in patient care. 2) Leverage Downstate's campus assets to build and extend collaborations and partnerships with our community for innovative public health, health disparities, and community-based participatory research informing preventive health, health promotion, and health care practice and policy. 3) Establish or expand unique research strengths and capacity that will enhance Downstate's role as a lead or partner in collaborative centers for clinical, public health, and basic research, including industry-sponsored projects. The first 40 proposals are currently under review, with plans to fund as many as 10 projects.

*2B.2e. The Cardiovascular Health Related Research PRIDE Summer Institute* provides intensive didactic and mentored research training to underrepresented minority faculty and those with disabilities engaged in cardiovascular health disparities research. The goals of the Institute are to: 1) select qualified underrepresented

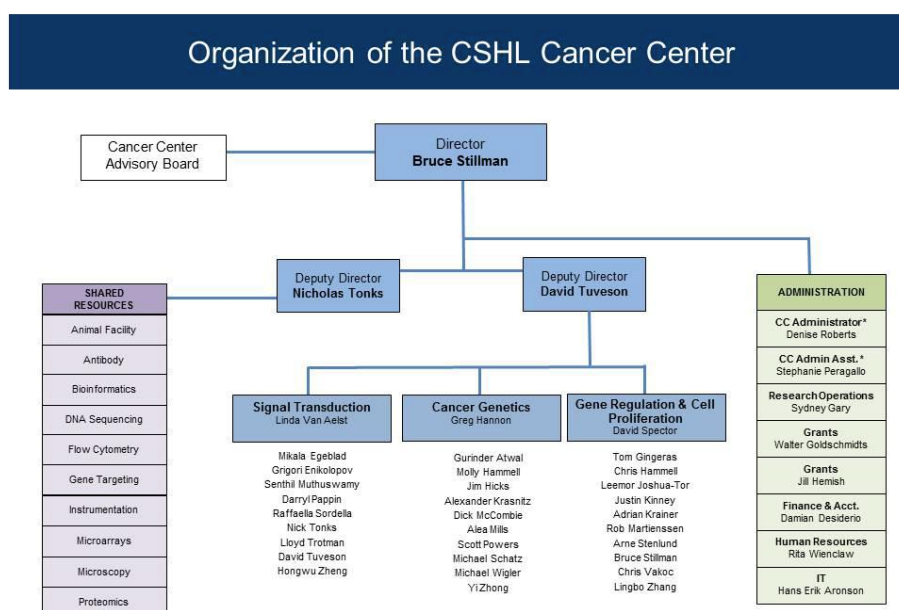
scientists who have great potential to contribute to the state of current knowledge in cardiovascular disease health disparity research, 2) train a diverse group of scientists in multidisciplinary research methods to address cardiovascular health disparities, 3) mentor underrepresented scientists in order to transition into independent researchers, and 4) provide underrepresented scientists with intensive individualized training and guidance in grant writing and peer review in order to enhance their capacity for success in their research careers. The PRIDE Summer Institute is a research career advancing opportunity at SUNY Downstate Medical Center that is funded by the National Heart, Lung, and Blood Institute (NHLBI). This mentored research program will address the difficulties experienced by junior investigators (with a terminal degree, e.g., MD, PhD, EdD) in establishing independent research programs and negotiating through the academic ranks. The PRIDE program is led by Dr. Mohamed Boutjdir, in the Department of Medicine, chaired by **Dr. Salifu**.

## 2C Cold Spring Harbor Laboratory Cancer Center.

*2C.1 The NCI designated Cancer Center at CSHL is a basic research facility and does not have direct access to cancer patients.* It is committed to exploring the molecular basis of human cancer through a focused multidisciplinary approach. As shown in Figure 1, the Cancer Center is directed by Dr. Bruce Stillman (see Letter of Support), Dr. **David Tuveson**, co-I on the CSHL Administrative Core and contact PI for pilot research project P2 serves as Deputy Director and oversees

the three research programs, including the Signal Transduction and the Cancer Genetics Program. The Cancer Center has ten Shared Resources including the DNA Sequencing Shared Resource.

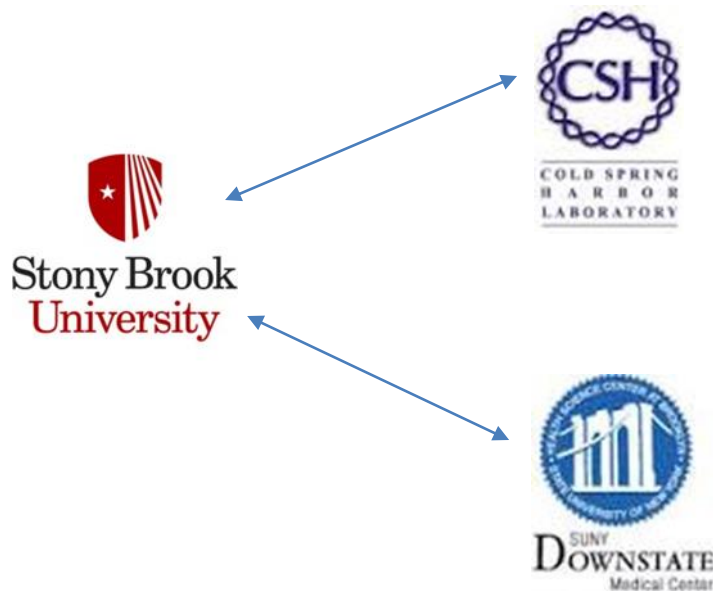
**Dr. McCombie**, contact PI for the CSHL P20 application, contact PI for the CSHL Administrative Core, the CSHL pilot project P1, and the CSHL Training and Education Program, is the Director of the DNA Sequencing Shared Resource and a member of the Cancer Genetics Program. **Dr. Mills**, co-chair of the Internal Advisory Committee, and Dr. **Wigler**, member of the Internal Advisory Committee are also members of the Cancer Genetics Program. The NCI-designated Cancer Center at CSHL has been at the forefront of developing new technologies to study the cellular and molecular biology of cancer.



**Figure 1. Organization of the CSHL Cancer Center**

*2C.1 Promoting recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies.* Cold Spring Harbor Laboratory (CSHL) has a long and exceptional history of conducting research and providing education in the biological sciences. Its Dolan DNA Learning Center, established in 1988, educates primary and secondary school students in genetics and provides innovative programs for science teachers. In addition, an Undergraduate Research Program which began in 1959, hosts exceptional undergraduates from around the world for a 10-week research experience each summer. CSHL welcomed its first class of students to The Watson School of Biological Sciences (WSBS), which is an accredited Ph.D., biology degree-granting institution. The WSBS awarded its first Ph.D. degrees in 2003. CSHL also offers courses at the postgraduate level, hosts international conferences, and organizes small conferences at the nearby Banbury Conference Center. More than 12,000 scientists visit the CSHL campus each year to participate in these programs.

## 2 D. Preexisting Partnerships between SUNY Stony Brook, SUNY Downstate and CSHL.



**Figure 2. Pre-existing partnerships between SUNY Stony Brook and CSHL and between SUNY Stony Brook and SUNY Downstate.** SUNY Stony Brook graduate programs allowed their students to have the option of rotating or performing their thesis work in CSHL research laboratories under CSHL research mentors instead of SUNY Stony Brook research mentors. The SUNY Health Network of Excellence established in late 2013 promoted discussions between SUNY Stony Brook and Downstate to conduct collaborative projects.

### 2D.1 SUNY Stony Brook and CSHL Partnership

**2D.1a. Joint graduate Ph.D. programs.** SUNY For over 30 years, CSHL has collaborated with Stony Brook University (SBU) to host SBU's graduate students to perform their dissertation research work with jointly appointed scientists in CSHL laboratories. In 1999, CSHL welcomed its first class of students to The Watson School of Biological Sciences (WSBS), which is an accredited Ph.D., biology degree-granting institution. The WSBS awarded its first Ph.D. degrees in 2003.

**2D.1b Development of collaborative translational projects between SUNY Stony Brook and CSHL investigators.** The SUNY Stony Brook GI Biobank, founded in 2010, facilitated collaborative interactions between SUNY Stony Brook clinicians and basic scientists with CSHL investigators. These collaborations arose from the complementary needs of SUNY Stony Brook clinicians and basic scientists to access a shared DNA sequencing resource and the needs of CSHL investigators to gain access to patient samples. One of the initial pilot projects to exploit this partnership was a pilot project initiated in 2011 and led by **Dr. Denoya**, a Hispanic Assistant Professor in Colon Rectal Surgery to develop high resolution methylation mapping in colon cancer in collaboration with **Dr. McCombie** at CSHL. Because the initial strategy was to use hybrid capture, RNA-Seq of colon cancer cell lines was conducted to determine the repertoire of probes for capture [5]. For a number of technical reasons, the strategy was shifted towards conducting reduced representation bisulfite sequencing. A number of experiments were conducted to establish the protocol and the depth of sequencing to obtain adequate coverage before using the pipeline to analyze the AA colon cancer samples assembled for **Dr. Jennie Williams** project and the development of **P1**. The recently generated methylation data [4] can be linked to existing parallel microRNA and mRNA profiles [3] generated from the same samples. These initial samples **Dr. Williams** analyzed in collaboration with **Dr. McCombie**, were however anonymous colon cancer samples obtained from the Washington University Siteman Cancer Center. These samples had limited associated metadata (race, anatomical position of tumor and stage). Because they were anonymized, they could not be linked back to the patients in order to obtain additional data on smoking, obesity, diabetes, and other cancer risk factors, or to longitudinal outcome (time to local recurrence, time to metastases, time to death).

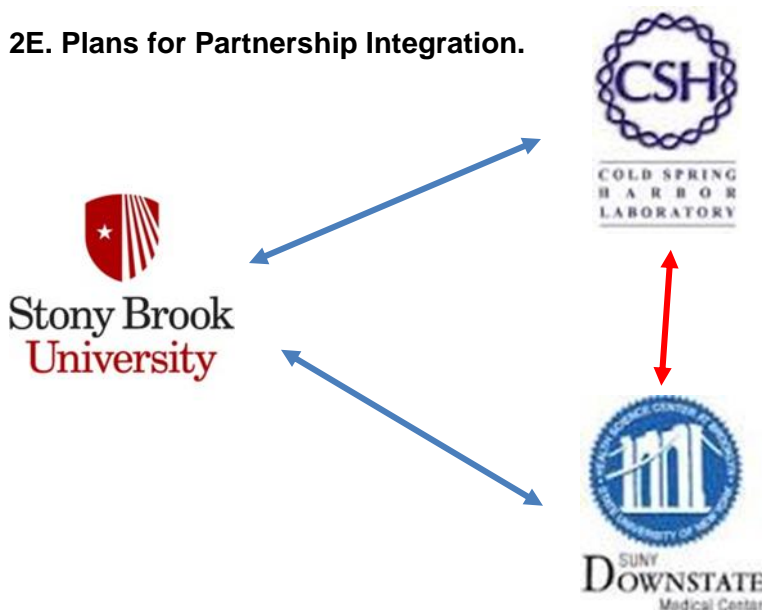
The development of **P2**, began after Dr. Tuveson's group presented their preliminary results on pancreatic organoids at a joint conference (January 2014) sponsored by the Stony Brook Cancer Center and attended by clinicians and basic scientists from SUNY Stony Brook, SUNY Downstate and investigators from CSHL.

## 2D.2 SUNY Stony Brook and Downstate Partnership.

**2D.2a SUNY Health Network of Excellence.** In 2013, SUNY and the Research Foundation for SUNY (RF) created the SUNY/RF Networks of Excellence to facilitate system-wide collaboration and partnerships to share expertise and assets for innovative advances in research. The Health Network of Excellence was designed to maximize the diverse strengths in biomedical research across the SUNY campuses and facilitate partnerships with academia, industry, and the community. **Dr. Mark Stewart** is one of the co-leaders of the Health Network of Excellence. **Dr. Ellen Li** served as one of three SUNY Presidential Fellows for the Health Network. Thus the mission of the SUNY Health Network is aligned with the mission of building the partnerships proposed in this application. The creation of this network prompted discussions between Dr. Li and Drs. **Stewart** and **Salifu** on developing a parallel GI Biobank at SUNY Downstate.

**2D.2b Collaborative translational projects between SUNY Stony Brook and Downstate.** Dr. **Salifu** identified **Dr. Laura Martello-Rooney** in the Division of Gastroenterology, who was actively engaged in translational research on pancreatic cancer, to lead the effort to begin prospective collection of GI cancer specimens at Downstate. Since these initial meetings, Since the original submission of this planning grant application, **Dr. Laura Martello Rooney** facilitated the transfer of 75 archived formalin-fixed paraffin embedded colon cancer tissue samples from African American patients for **Dr. Jennie Williams** to analyze microRNAs that are differentially expressed. Since the submission of the original application for this planning grant, **Dr. Jennie Williams** is in the process of submitting an RO1 with **Dr. Martello-Rooney** and **Dr. McCombie** as co-investigators that includes reduced representation bisulfite sequencing, in addition to RNA-Seq of mRNA and miRNA profiles of African American colon cancer and adjacent normal colon.

## 2E. Plans for Partnership Integration.



**Figure 3. Partnership Integration.** We plan to strengthen existing partnerships between SUNY Stony Brook and CSHL and between SUNY Stony Brook and SUNY Downstate. We plan to create partnerships between CSHL and SUNY Downstate.

Partnership integration will strengthen existing partnerships between SUNY Stony Brook and CSHL, and between SUNY Stony Brook and developing a new partnership between SUNY Downstate and CSHL will take place at every level of the P20 organization (see **Figure 3** and **Figure 4**). – Integration will center around the development of a parallel GI Cancer BioBank at SUNY Downstate using the same standard operating procedures as the GI Biobank at SUNY Stony Brook and planning the development of an integrative biomedical informatics platform that will link coded de-identified patient samples with i) coded deidentified rigorously curated longitudinal clinical metadata with defined clinical endpoints and ii) downstream data (e.g. molecular and histological imaging data) generated from the patient samples. The GI BioBanks will play a central role in preserving the links between specimen, clinical metadata and downstream molecular and histological data. As part of this planning process an essential first step is to develop a common list of elements to include in the clinical metadata and a common vocabulary. Integrations will also center around developing a novel integrated cross-institutional Scholars in Biomedicine Program aimed at training doctoral trainees in translation

science/clinical research on cancer where special emphasis will be placed on how to translate 'bench-to-beside' research to the community practice setting for cancer prevention, diagnosis and treatment health disparity.

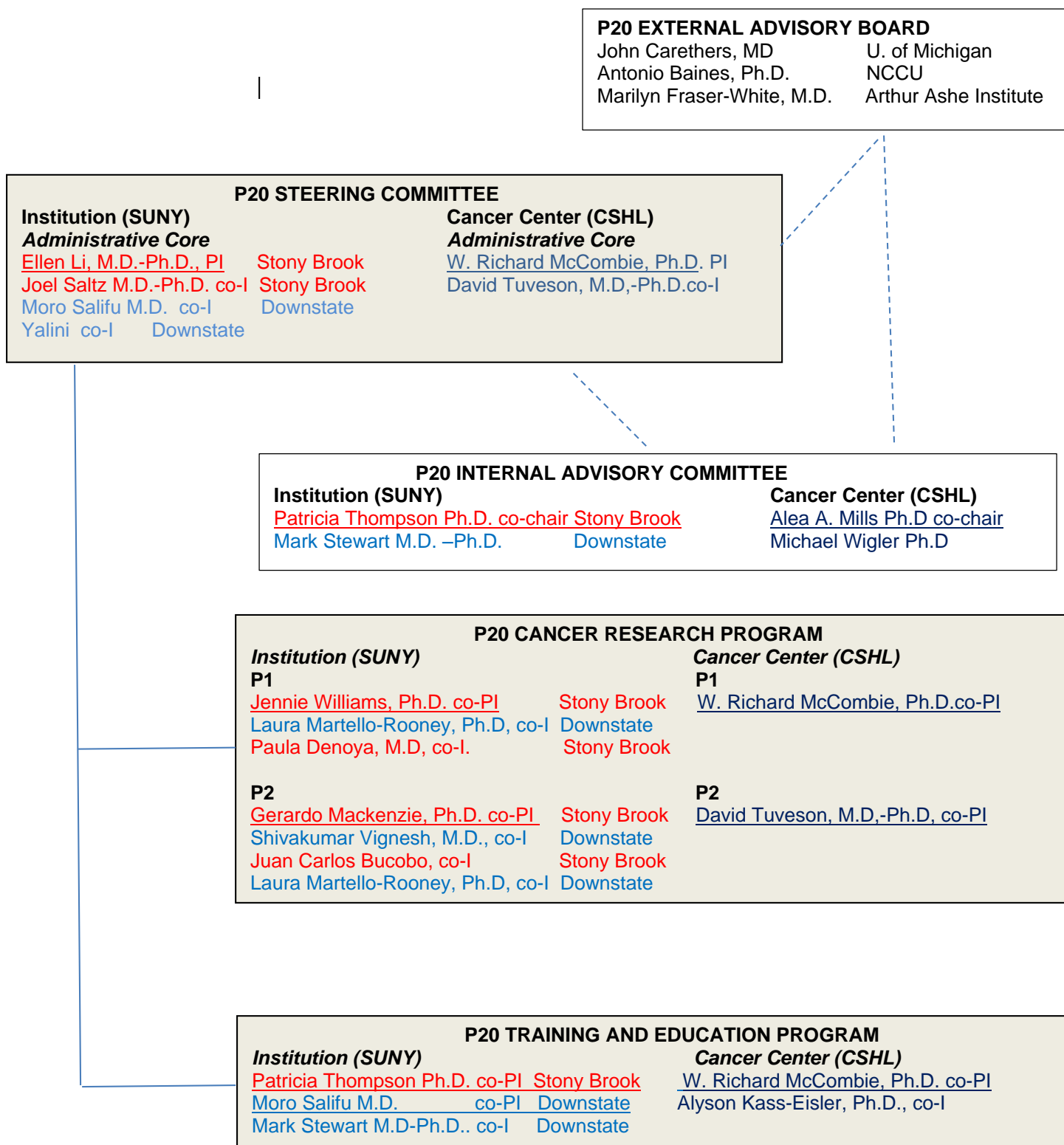


Figure 4. Organizational Chart of P20 Scientific and Administrative Leadership.

### 3. Scientific and Administrative Leadership, and Administrative Core.

As shown in **Figure 4**, the SUNY (Institutional) and CSHL (Cancer Center) Administrative Cores will be combined into a central **Steering Committee**, which will be co-chaired by the contact PIs (Drs. **Li** and **McCombie**) of the partnering P20 planning grant applications. **Dr. Li** will coordinate the development of the SUNY Downstate GI BioBank with the activities of the SUNY Stony Brook GI BioBank (which has amassed tissues, blood and other fluids from > 600 subjects and includes >100 subjects with paired colorectal cancer and adjacent normal tissues). To promote collection of URM biospecimens, **Dr. Moro Salifu** (SUNY Downstate, the co-PI on the SUNY, will coordinate the activities of the Brooklyn Health Disparities Center with the development of the SUNY Downstate GI Biobank. **Dr. McCombie** and **Dr. Tuveson** will coordinate joint pilot research projects P1 and P2 which require access to the DNA Sequencing Shared Resource at CSHL. We have added two biomedical informaticians to the leadership team, **Dr. Joel Saltz**, founding Chair of the Department of BioMedical Informatics at SUNY Stony Brook and **Dr. Yalini Senathirajah**, Assistant Professor of Biomedical Informatics at SUNY Downstate, who will help plan incorporating the same data elements and controlled vocabulary in order to facilitate transfer of information between the three institutions, investigators throughout the SUNY system, and the larger cancer research community. The **Steering Committee** will meet monthly to oversee planning of a parallel GI Biobank at SUNY Downstate, and the development of an integrative bioinformatics platform, and the Cancer Research and Training and Education programs.

The **Steering Committee** will be advised by the **Internal Advisory Committee** that is co-chaired by **Dr. Thompson** (SUNY Stony Brook) and **Dr. Tuveson** (CSHL) and will also include a representative from SUNY/Downstate, **Dr. Mark Stewart** and a representative from CSHL, **Dr. Michael Wigler**. The Internal Advisory Committee will meet quarterly to review progress on the Administrative Core, the Cancer Research Program and the Training and Education Program.

The **Steering Committee** will also be advised by a three member **External Advisory Board**, which will meet annually during the Cancer Health Disparities symposium to review progress on the Administrative Core, the Cancer Research Program and the Training and Education Program. .

## 4. Cancer Research Program

**4A. Pilot Research Project 1 (P1).** Two SUNY medical campuses (SUNY Stony Brook and SUNY Downstate) serving underrepresented minority communities with cancer health disparities are partnering with the NCI designated Cancer Center at the Cold Spring Harbor Laboratories (CSHL) to evaluate biological and genetic differences in colorectal cancers that may link to differences in cancer incidence and outcome observed in racial and ethnic minorities. We plan to develop a SUNY Downstate GI BioBank that will greatly augment the representation of underrepresented minorities in the collection of biospecimens that will use the same standard operating procedures currently in place at the SUNY Stony Brook GI BioBank. Furthermore the clinical metadata elements collected at SUNY Downstate will be the same and utilize a common controlled vocabulary that is used by the SUNY Stony Brook GI BioBank. To increase community participatory research among racial and ethnic minority populations, we plan to leverage the resources and expertise of the SUNY Downstate Brooklyn Health Disparities Center (led by **Dr. Moro Salifu**) in developing community education and outreach programs in underserved communities with a high proportion of racial and ethnic minorities (>70% African Americans). In P1, we propose to generate genomic and epigenetic profiling data of colon cancers using the NCI supported CSHL Shared DNA Resource Core directed by **Dr. Dick McCombie** (CSHL contact PI for P1) Generating the sequencing data will provide immediate feedback to the Downstate GI BioBank with respect to monitoring Q/A for their collection efforts. This genomic and epigenomic data will be linkable to parallel microRNA and RNA-Seq mRNA profiling and immunohistochemical data generated on the same coded deidentified samples by **Dr. Jennie Williams** (SUNY contact PI for P1) and **Dr. Denoya** (SUNY co-I). We anticipate that making the linked datasets available on the integrated biomedical informatics platform being developed by this proposed P20 project will facilitate sharing of these extremely valuable datasets with the larger cancer research community.

**4B. Pilot Research Project 2 (P2)** We propose to test the hypothesis that genetic and gene expression alterations underlie the increased incidence, mortality, and treatment resistance observed in under represented minorities (URMs). A new tissue model system, organoids, which was developed in the **Tuveson** laboratory, will create a living BioBank of both resectable and unresectable URM pancreatic cancers, and allow the evaluation of the cell autonomous contribution to the increased risk of pancreatic cancer in URM [6]. This hypothesis will be tested by 1.) Establishing a cohort of URM pancreatic tumor organoids from endoscopic ultrasound guided

fine needle core biopsy samples obtained at SUNY Downstate using procedures developed between SUNY Stony Brook and CSHL. 2.) Perform next generation sequencing (RNA and DNA sequencing) on the URM organoids to delineate the molecular properties of the organoids. This data will be compared with data obtained on non-URM organoids generated by a collaboration between SUNY Stony Brook and CSHL funded by separate funding sources. 3.) Determine whether there are innate cell biological differences between URM and non-URM organoids after measuring tumor progression in an orthotopic transplant model conducted at SUNY Stony Brook (**Dr. Gerardo Mackenzie**).

### **5. Training and Education Program**

We propose to address critical research and translation gaps for Cancer Health Disparities (CHD) by leveraging our strengths through a unique 'Scholars in Biomedical Sciences for CHDs' program (SBMS-CHD). The overarching goal and we believe a major solution to address CHDs is to successfully train PhD and MD/PhD scientists in cancer research that integrates concepts of research translation from the 'bench-to-bedside' academic model to cancer care delivery in community practice. The specific goal of this planning period will be to develop and test the effectiveness of a training environment aimed at enhancing knowledge of CHDs among established faculty mentors and to engage and empower, through knowledge and training in CHDs, a cohort of exceptional cancer research scientists with an interest in conducting high-quality research aimed at addressing biological and clinical causes of CHDs.

### **6.Planning and Evaluation**

We have made significant progress since the initial submission of this P20 planning grant application, in terms of initial planning for the joint SUNY-CSHL Cancer Research Program and the Training and Education Program. We have obtained IRB approval at SUNY Downstate and Stony Brook for pilot research project P1 and P2. We have begun planning the development of the Integrative Scholars in BioMedical Sciences in Cancer Health Disparities by meeting with the founding Director (Dr. Stella Tsirkas) and clinical co-Director (Dr. Yang of the existing Scholars in Biomedical sciences at SUNY Stony Brook.

The Steering Committee along with the Internal Advisory Committee will review progress of the two pilot projects in the Cancer Research Program and the Training and Education Program on a quarterly basis. The External Advisory Committee will meet annually to review progress. Based on these discussions, priorities and resources may be shifted in years 2-4 towards new initiatives, based on progress or lack of progress, successful acquisition of additional extramural funding of some of the objectives of the Pilot Projects or the Training and education Programs. The monthly GI Cancer Research meetings and the annual Symposium on Cancer Health Disparities will provide the leadership with information of potential alternative pilot research projects that could be funded if larger research awards are secured for the existing pilot projects.

## **Protection of Human Subjects**

As part of this proposal, human three-dimensional organoids, will be generated from normal human pancreatic tissue or human pancreatic ductal adenocarcinomas. Human normal pancreatic tissue will be obtained from de-identified human autopsy samples used to isolate material for pancreatic islet transplantation. Because this tissue comes from deceased humans, these samples do not meet the criteria for human subject research according to federal regulations. Nonetheless, we have approval through the Cold Spring Harbor Laboratory IRB under the project title "[556949-1] Isolation and analysis of normal pancreatic exocrine tissue," and a copy of this approval letter is included in the Appendix of this proposal.

Fine needle aspirate from human pancreatic adenocarcinoma specimens will be obtained from de-identified patients. We have approval for this through the Cold Spring Harbor Laboratory IRB, under the project title [588966-1] "Collection of Tissue, Blood and Other Specimens from Patients [Stony Brook Medicine]" and a copy of this approval letter is included in the Appendix of this proposal. Because all samples we receive will be de-identified, the Cold Spring Harbor Laboratory IRB has unanimously agreed that the proposed research qualifies for an exemption under 45 CFR 46.101 (b) (4).

## **Inclusion of Women and Minorities**

For pancreatic cells isolated from human autopsy samples, de-identified samples will be collected from deceased males and females of any ethnic group as they are available and meet the criteria for human islet cell transplant. Only after pancreatic islet cells suitable for transplant have been removed from these samples do we receive them.

For pancreatic tumor specimens taken from living patients, de-identified tumor tissue will be obtained from patients being treated for pancreatic ductal adenocarcinoma at SUNY medical institutions. Our study will aim to collect samples from males and females of under represented minorities to serve as the material for this study.

## **Inclusion of Children**

Pancreatic ductal adenocarcinomas are almost never found in children so no children will be used in this study.

## PILOT RESEARCH PROJECT P2 -VERTEBRATE ANIMALS

### 1. **Proposed use of animals**

We will use mice as described in the Pilot Research Project Research Strategy section. Animal numbers and their planned use in Pilot Project 2 are listed below.

#### **Specific Aim #1: Preparation of URM pancreatic cancer organoids**

- No animals needed

#### **Specific Aim #2: Molecular characterization of URM pancreatic cancer organoids**

- No animals needed

#### **Specific Aim #3: Tumor progression studies of URM pancreatic cancer organoids**

- **Orthotopic tumor (T) organoid implants [See below a):**
  - Four independent experiments: female SCID mice 5-6 wks old
  - Two groups per experiment: a) URM; b) Non-URM (same disease stage).
  - Two time-points: 1-month post implantation and 4-month post implantation.
  - Six animals per group per time-point

Total = **96 mice** (for all four independent experiments)

### **Detail description of the proposed studies**

#### **a) Orthotopic implantation of pancreatic T organoids**

SCID mice represent a widely used animal model for such purposes. These mice have no immune reaction to human cells or tumors when they are implanted in them (ordinary mice reject them). This animal model provides the opportunity to assess the tumor progression studies in URM and Non-URM pancreatic cancer organoids.

### **Experimental procedures**

#### **Implantation of URM and Non-URM tumor organoids into SCID mice**

1. For the orthotopic engraftment of human T organoids, mice are anesthetized using Isoflurane (5% induction, 2% maintenance), and Ketrolac (5 mg/kg), subcutaneously administered.
2. An incision is made in the left abdominal side.
3. URM and Non-URM organoids ( $1 \times 10^6$  cells/mouse) are prepared either from cultures or from cryopreserved stocks. In the case of cryopreserved stocks, organoids are thawed in HEPES (1x, Invitrogen), Glutamax (1x, Invitrogen), and penicillin/streptomycin (1x, Invitrogen), in AdDMEM/F12 media and stabilized for 4 hr at 37°C in 5% CO<sub>2</sub>. Organoids are washed with ice-cold PBS, physically broken into pieces by triturating through fire-polished glass Pasteur pipettes, and finally resuspended in 50 µl of Matrigel (Matrigel, BD) diluted 1:1 with cold PBS.
4. The organoid suspension is injected into the tail region of the pancreas using insulin syringes (29 Gauge). Successful injection is verified by the appearance of a fluid bubble without signs of intraperitoneal leakage.
5. The abdominal wall is then sutured with absorbable Vicryl suture (Ethicon), and the skin is closed with wound clips (CellPoint Scientific Inc.).
6. Mice are euthanized at the indicated time points (one month and four-month implantation).

### **Anesthesia**

**Agent:** Isoflurane: 5% for induction; and then 2% for the maintenance during the procedure

After surgery, The animals will be monitored on the heating pad until they begin to move. Once movement is observed, usually 30 to 45 minutes later, the animals will be placed in their original sterile isolation cages. Before departing for the day, the animals will be observed once more to ensure that no problems arose.

*Monitoring parameters and frequency:* Observation until the animals are awake and moving around.

*How recovery monitoring will be performed:* Visual observation.

### Analgesia

Topical lidocaine will be provided immediately post-op. All animals will receive one dose of Ketorolac 5 mg/kg SQ. If they continue showing signs of pain, we will continue administering Ketorolac until pain ceases.

Animals will be checked to monitor for the presence of pain, discomfort or distress until they are awake and moving around. After that, we will observe the animals visually daily.

## **2. Justification of use of animals:**

There are two key advantages in using human T organoid models for tumor progression studies: **1)** T organoids can propagate rapidly, operating on a time scale of weeks instead of the years, as it takes to establish patient derived xenografts; and **2)** Tumor organoids develop a surrounding desmoplastic reaction, better mimicking what occurs in human PDA. This is in contrast to what is observed in two-dimensional human PDA cell lines, which lack of stromal reaction. We propose to use URM and non-URM pancreatic cancer organoids orthotopically transplanted into immunodeficient mice (SCID mice), to determine if cellular behavior differs between URM and non-URM PDA.

Statistical power calculations: With 6 animals or tumors per group per time-point, we have 82% power to detect a 34% difference in tumor growth between URM and NON-URM assuming a 1-tailed  $\alpha=0.05$  t-test. Statistical Analysis: Tumor weight will be compared among the experimental groups using one-way ANOVA followed by Tukey's method of multiple comparisons.

## **3. Veterinary care of the animals:**

Animals are housed in one of our state-of-the-art Animal Facilities at Stony Brook University. The Division of Laboratory Animal Services (DLAR) at Stony Brook University is administratively centralized but the services are campus-wide. The main facility is on the ground level of the Health Sciences Center. This is a 36,500 sq. ft. facility that provides the administrative space for the DLAR, diagnostic laboratory, necropsy, X-ray unit, gamma camera, a teaching surgery room used primarily for non-survival procedures, a section of four large modern survival surgery suites with adjacent locker change rooms, scrub room pre-op and post-op rooms. There are two autoclaves in the surgery area and four in another location. Gas sterilization is provided by central sterilizing. The facility has housing suitable for most any species one would need to use.

The DLAR is staffed with people of appropriate education and experience. There is seven day per week animal care with two veterinarians rotating after hours, weekend and holiday call. The trainings required by the Office for Protection from Research Risks (OPRR) and the Animal Welfare Act are provided by the Director of the DLAR and his assistants. The University Assurance statement to OPRR has been accepted and the IACUC is duly constituted and meets every two weeks. The DLAR is fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). All experimental protocols are submitted to IACUC for approval. A detailed description of justification of the use of animals, the choice of species, and the number of animals to be used is given in "Experimental Procedures." A fully equipped diet laboratory and low temperature storage facility for pre-mixed diets are available. Animals are cared for seven days a week every day of the year. All animals are quarantined for 10 days prior to their transfer to a holding room. During this time, they are carefully screened for internal and external parasites, respiratory and fecal pathogens, blood parasites, dermatophytes and viruses. A selected population is necropsied and a histopathological study performed. All animals will be maintained under controlled conditions (21°C and 50% relative humidity in a 12h-light/dark cycle). They will be fed *ad libitum* with free access to water.

All animals are examined at least twice daily. Weights are recorded once weekly and any untoward findings are reported to the veterinarian in charge.

## **4. Procedures ensuring comfort of animals:**

During the surgical procedures described above, the animals will suffer discomfort. To minimize the discomfort, we will anesthetize the mice (please see above for details). Furthermore, animals will be checked

twice daily to monitor for the presence of pain, discomfort or distress after the surgery. They will receive analgesia for this purpose (ketorolac and lidocaine). Any animal that continues showing signs of pain, will be administered with extra analgesia as needed. Moreover, we will check for potential signs of infection in the surgical implant site. If we observe any signs of infection, the animals will be treated with antibiotics. If we observe any signs of suffering, we will euthanize the sick animals.

### **5. *Methods of euthanasia***

CO<sub>2</sub> euthanasia will be used and it has been selected for its simplicity and comfort to the animals. The method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. Following euthanasia with CO<sub>2</sub>, we will perform cervical dislocation to ensure death of the animals.

## OVERALL – REFERENCES

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**Stony Brook Medicine**

Kenneth Kaushansky, M.D., M.A.C.P.  
Senior Vice President, Health Sciences  
Dean, School of Medicine

March 11, 2015

Ellen Li, M.D., Ph.D.  
Director, Division of Gastroenterology and Hepatology  
Stony Brook Medicine  
Stony Brook, NY 11794-8173

**Re: Feasibility Studies to Build Collaborative Partners in Cancer Research**

Dear Dr. Li,

I am delighted to write this letter in support of your proposal entitled "Partnership to Study Racial/Ethnic Differences in GI Cancer Biology", which brings together investigators from Stony Brook Medicine with investigators from Downstate Medical Center and investigators at the Cold Spring Harbor Laboratories (CSHL) to study health disparities in GI cancers. This project is both innovative scientifically and clinically important, and these partnerships will be a vital component in Stony Brook Cancer Center's plan to achieve NCI designation.

I also applaud your efforts in leading the organization of a GI Cancer Interest Group around the collection process and in collecting important GI tissue biospecimens. As you know, Stony Brook University has invested heavily and will continue to invest to support clinical and translational cancer research. For example, we will complete construction for our new Medical and Research Translation (MART) facility, a 240,000 square-foot state of the art building which will house eight floors devoted to imaging, neurosciences and cancer research, including 25 cancer biology-oriented labs.

Stony Brook University is deeply committed to addressing racial/ethnic disparities in education and healthcare. The number of Stony Brook University undergraduates completing a bachelor's degree in biological, biomedical computer/mathematics, and health fields has increased from approximately 1,400 per year to 2,000 per year over the past 10 years. The proportions of students that were Black or Hispanic in these fields were approximately 10% and 8% respectively. The number of Stony Brook University graduate students completing a doctoral degree in these fields has remained constant at roughly 200 per year over the past 10 years. The proportions of students that were Black and Hispanic was approximately 5% and 3%, respectively. We want to improve the participation of underrepresented minorities in biomedical research and we will provide matching funds for your Training and Education program which builds off the pilot Scholars in Biomedical Sciences program that we started two years ago, and

for travel costs for the three External Advisory Board members (\$220,000 over 4 years). This program will help underrepresented minority doctoral students gain additional mentoring (research and clinical) and training in conducting translational research.

I believe that all of the projects proposed in your application will not only have an impact on our understanding of the biological basis for differences in GI cancer incidence and outcomes in underrepresented minorities, but will also lead to the development of more personalized approaches to the treatment of GI cancers, and hopefully progress in the elimination of health disparities in the outcomes of these deadly diseases.

Sincerely,



Kenneth Kaushansky, M.D.  
Senior Vice President, Health Sciences  
Dean, School of Medicine



SUNY  
**DOWNSTATE**  
Medical Center

**John F. Williams, Jr., MD, EdD, MPH, FCCM**  
President

University Hospital of Brooklyn  
College of Medicine  
School of Graduate Studies  
College of Nursing  
College of Health Related Professions  
School of Public Health

March 11, 2015

Ellen Li, MD, PhD  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine  
Stony Brook, New York 11794  
Re: Collaborative Partners in Cancer Research

Dear Dr. Li,

I am an enthusiastic supporter of your project entitled, "Partnership to Study Racial/Ethnic Differences in GI Cancer Biology," which will partner investigators from Downstate Medical Center with your group at Stony Brook Medicine and investigators at the Cold Spring Harbor Laboratories. This team will be able to address significant issues with regard to GI cancer detection, especially as they impact ethnic minority patients in the New York City / Long Island area.

Downstate continues to strengthen its commitment to addressing health disparities, and joining you on this GI cancer project will be enormously important for our community of patients. I believe that the interaction of your group with Downstate's own NIH-funded Health Disparities Center will allow us to have even greater impact through our close community ties. As results become available, we will be able to keep our community members up-to-date on this exciting project.

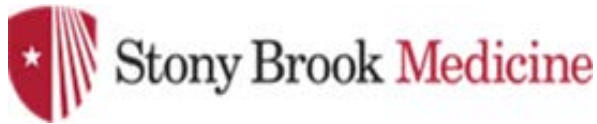
I have a deep personal interest in advancing research in key areas where health disparities have significant impact on patient lives. I recently initiated a Health Disparities Research Fund to stimulate projects such as the one you are proposing. Our campus-wide commitment to disparities research is reflected in the fact that 40 interdisciplinary teams responded to our first call for proposals.

An experienced team with mature research questions is exactly what I hope we can develop in each of the different key areas struggling with disparities in diagnosis, treatment, and access. I view your group as a model for a genuinely translational research team.

I am pleased to see that our School of Graduate Studies has committed the resources to support up to two students annually in this program. This is an excellent symbol of our campus support. I am glad to help in any other ways that I can. Good luck with the proposal and we look forward to growing our partnership for the vital questions in cancer diagnosis and care.

Best wishes,

John F. Williams, MD, EdD, MPH, FCCM  
President



**Vincent W. Yang, M.D., Ph.D.**

*Simons Chair of Medicine*

*Professor, Department of Medicine*

*Professor, Department of Physiology and Biophysics*

*Stony Brook University*

*Stony Brook, New York*

March 6, 2015

Ellen Li, M.D., Ph.D.

Chief, Division of Gastroenterology and Hepatology

Stony Brook Medicine

**RE: Feasibility studies to Build Collaborative Partners in Cancer Research**

Dear Dr. Li (Ellen):

I am delighted to write this letter in support of the Training and Education program section of your planning grant application entitled "Partnership to study racial/ethnic differences in GI cancer biology" in response to PAR-14-152 "Feasibility studies to Build Collaborative Partners in Cancer Research".

As the Simons Chair of Medicine, my mission is to increase basic and translational research in this department. A major focus of my research group's work is on Kruppel-like factors in colon cancer but have recently branched out to investigate their role in pancreatic cancer. I have watched you develop the GI Biobank infrastructure for effective collection of colonic and pancreatic tissues linked to blood, stool and rigorously collected clinical metadata. The linked 'omics colon cancer datasets generated in pilot project P1 and the pancreatic organoids generated in pilot project P2, will be of great interest not only to my research group but also to investigators in the larger research community.

As you know I serve as the clinical co-Director of the Scholars in Biomedical Sciences (SBMS) for Stony Brook University with Dr. Stella Tsirkas, which was established two years ago with support from the Dean of the School of Medicine, the Dean of the Graduate School and the Provost. I look forward to working with the leadership team for the Training and Education program, Drs. Mark Stewart, Patty Thompson and Moro Salifu, to incorporate into SBMS the additional four slots your program will be providing.

As you know I am also co-PI of an NCI R25 program that partners underrepresented minority undergraduates with research mentors in the American Gastroenterology Association. I have trained --- graduate students and I am very enthusiastic about the opportunity for my students to participate in the expanded Scholars in Biomedical Sciences focusing on Cancer Health Disparities.

I look forward to attending and will certainly encourage members of my research group to attend the annual Cancer Health Disparities seminar organized by the Training and Education program will be widely attended not only by the faculty and students involved in the SBMS program but by other faculty and students from life sciences graduate programs.

Best of luck with your application.

A handwritten signature in blue ink, appearing to read "Vincent W. Yang".

Vincent W. Yang, M.D., Ph.D.

Stony Brook University Medical Center | Department of Medicine  
Health Sciences Center T-16, Room 20, Stony Brook, NY 11794-8160  
Tel: (631) 444-2066 Fax: (631) 444-3144 Email: [vincent.yang@stonybrookmedicine.edu](mailto:vincent.yang@stonybrookmedicine.edu)



*Styliani E. Tsirka, PhD*  
*Professor, Pharmacological Sciences*  
*Director, Scholars in BioMedical Sciences Program*  
*Vice Provost for Faculty Affairs*

Dr. Ellen Li  
Chief, Division of Gastroenterology and Hepatology

Dear Dr. Li (Ellen) –

I am delighted to write this letter in support of the Training and Education program section of your planning grant application entitled "Partnership to study racial/ethnic differences in GI cancer biology" in response to PAR-14-152 "Feasibility studies to Build Collaborative Partners in Cancer Research". As you know I serve as the director of the Scholars in Biomedical Sciences (SBMS) for Stony Brook University, which was established two years ago with support from the Dean of the School of Medicine, the Dean of the Graduate School and the Provost. I look forward to working with the leadership team for the Training and Education program, Drs. Mark Stewart, Patty Thompson and Moro Salifu, to incorporate into SBMS the additional four slots your program will be providing.

I am confident that the annual Cancer Health Disparities seminar organized by the Training and education program will be widely attended not only by the faculty and students involved in the SBMS program but by other faculty and students from life sciences graduate programs.

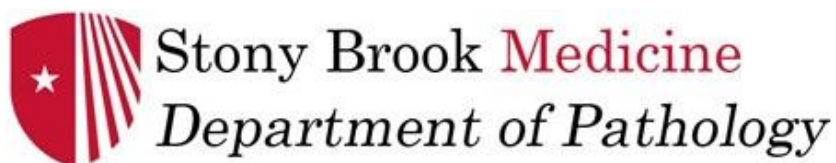
The Training and Education program you propose in your application will intersect very well with the objectives of SBMS and the training of our students. Dr. Vincent Yang, the clinical co-director of the SBMS program, and I are looking forward to interacting with you and the faculty of your partnership, and I am certain that our students will be the winners of this interaction!

Best of luck with your application.

Kind regards,

A handwritten signature in black ink, appearing to read "Stella Tsirka".

Stella Tsirka



March 15, 2015

Dr. Ellen Li  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

RE: Feasibility Studies to Build Collaborative Partners in Cancer Research

Dear Dr. Li (Ellen) –

This letter confirms my support of your P20 grant application entitled “1/2: Partnership to study racial/ethnic differences in GI cancer biology”, which you are submitting in collaboration with Cold Spring Harbor Laboratories who will be submitting the accompanying application, “2/2: Partnership to study racial/ethnic differences in GI cancer biology”, in response to PAR-14-152 entitled “Partnerships in cancer research”.

I have enjoyed working with you over the past several years on streamlining the consenting and collection process for GI cancer tissues linked to blood and stool. More recently, I applaud the teamwork that has been developed between the surgical staff, The GI Biobank staff and that of the Stony Brook Cancer Center BioBank staff in coordinating the rapid transport of pancreatic cancer tissue to multiple investigators, including Dr. Tuveson and Dr. Gerardo Mackenzie, as well as collecting parallel fluid (blood and urine) samples. I believe that we have developed a very efficient model for the development of a parallel Biobank at SUNY Downstate.

We have also collaborated to support Dr. Jennie Williams and Dr. McCombie’s projects on colon cancer biomarkers, as they related to racial differences in colorectal cancer clinical outcome.

In addition to my role as an experienced surgical pathologist with expertise in the histologic assessment of colorectal tumors, I chair the Department of Pathology, I lead a cancer biomarkers research program, serve as the Director of the Research Histology Core Lab, and am the senior advisor to the Stony Brook cancer Center Biobank. The full resources of the Department will be made available to support the needs of your proposed research projects. More specifically I am expressing my willingness to assist with Dr. Mackenzie with reviewing the histology and immunochemical studies he proposes to conduct to assess tumor progression of orthotopically transplanted pancreatic organoids in pilot project **P2**.

I also look forward to working with you, and other members of my department, Dr. Patricia Thompson and Dr. Joel Saltz, on planning the development of an integrative biomedical informatics platform that will link longitudinal clinical metadata to patient samples stored in the Biobank with molecular and histological data generated from the patient samples.

Stony Brook, NY 11794-8691 Telephone: 631.444.3000 Fax: 631.444.3424

I am very interested in participating as a Research Mentor for the proposed Scholars in BioMedical Sciences in Cancer Health Disparities. The focus of my research laboratory is on gynecological cancers. Black women have a much higher mortality from cervical cancer than other racial groups.

Best wishes for the success of your application; I'm looking forward to continuing to work with you.

Sincerely,

A handwritten signature in black ink, appearing to read 'Ken Shroyer', with a long, sweeping horizontal line extending to the right.

Kenneth R. Shroyer, MD, PhD  
The Marvin Kuschner Professor and Chair of Pathology  
Basic Science Tower, level 9, room 140 Stony  
Brook Medicine

<http://www.stonybrookmedicalcenter.org/pathology/faculty/shroyer/>



*School of Medicine*

*Professor of Medicine and Dean  
of Research*

**Lina M. Obeid, M.D.**

March 15, 2015

Dr. Ellen Li  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

RE: Feasibility studies to Build Collaborative Partners in Cancer Research

Dear Dr. Li (Ellen) –

I am delighted to write this letter in support of the Training and Education program section of your planning grant application entitled "Partnership to study racial/ethnic differences in GI cancer biology" in response to PAR-14-152 "Feasibility studies to Build Collaborative Partners in Cancer Research". As Dean of Research overseeing the Office of Scientific Affairs at Stony Brook Medicine I am delighted to participate in building collaborative partnerships with SUNY Downstate and CSHL, particularly as Stony Brook Medicine seeks NCI-designation for its own Cancer Center.

I am interested in serving as a research mentor for the Scholars in Biomedical Sciences in Cancer Health Disparities. My own research focuses on the role of sphingolipids in regulating cancer growth. My work on elucidating the interactions between nutrition, chronic inflammation, sphingolipid metabolism and colon cancer is potentially very relevant to racial ethnic differences in colon cancer biology. We were very interested in hearing about Dr. Jennie Williams' work on miRNA and more recently potential DMR between African American and Caucasian colon cancers at the monthly GI Cancer Research meetings. My research group will be very interested in accessing the 'omics datasets generated in pilot project P1 and potentially building on that database by conducting parallel metabolomic studies on the SUNY Stony Brook and Downstate GI Biobanks.

I look forward to attending and will certainly encourage members of my research group to attend the annual Cancer Health Disparities symposium organized by the Training and Education program will be widely attended not only by the faculty and students involved in the SBMS program but by other faculty and students from life sciences graduate programs.

Best of luck with your application.

Sincerely,

A handwritten signature in black ink, appearing to read "Lina M. Obeid, M.D.", with a stylized flourish at the end.

Lina M. Obeid, M.D.  
Professor of Medicine  
Dean of Research, School of Medicine



SUNY  
**DOWNSTATE**  
Medical Center

University Hospital of Brooklyn  
College of Medicine  
School of Graduate Studies  
College of Nursing  
College of Health Related Professions

Department of Anatomy  
and Cell Biology

Feb. 28, 2015

Mark Stewart  
Dean  
School of Graduate Studies  
SUNY Downstate Medical Center

Dear Mark,

I would be happy to serve as mentor for the P20 grant application that you are spearheading to submit. As you know I have mentored several MD/PhD and PhD students and therefore have significant credentials to continue the training of young MD/PhD and PhD students. Our laboratory focuses on intestinal lipid absorption and its regulation by diet, circadian rhythms, unfolded protein response, microRNA etc. Therefore, student will obtain a rich and diverse training in the laboratory covering various aspects of molecular biology and metabolism. Do not hesitate to ask if need more information.

With best wishes,

A handwritten signature in blue ink, appearing to read "M. Hussain", with a large, stylized initial "M" and a horizontal line extending to the right.

M. Mahmood Hussain, PhD  
Professor  
SUNY Downstate Medical Center

State University of New York Downstate Medical Center

450 Clarkson Avenue, Box 5, Brooklyn, NY 11203-2098 • Phone 718 270-1014 Fax 718 270-3732

**Stony Brook University  
Health Sciences Center**

*School of Medicine*

Department of Pathology

March 16, 2015



Dr. Ellen Li  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

RE: Feasibility Studies to Build Collaborative Partners in Cancer Research

Dear Dr. Li (Ellen) –

I am delighted to write this letter in support of the Training and Education Program section of your planning grant application entitled "Partnership to study racial/ethnic differences in GI cancer biology" in response to PAR-14-152 "Feasibility studies to Build Collaborative Partners in Cancer Research".

I am interested in serving as a research mentor for the Scholars in Biomedical Sciences in Cancer Health Disparities. My own research focuses on micro-RNA biomarkers for response to chemotherapy. Consequently, my research group will be very interested in accessing the 'omics datasets generated in pilot project P1. I would be very interested in determining whether the biomarkers I have identified are differentially expressed in African American compared to Caucasian colon cancer tissue samples. I am therefore very interested in accessing samples in the parallel SUNY Downstate GI Biobank that this planning grant is trying to develop.

I currently participate in the monthly GI Cancer Research meetings and I look forward to attending and will certainly encourage members of my research group to attend the annual Cancer Health Disparities symposium organized by the Training and Education program.

Best of luck with your application.

Sincerely,

A handwritten signature in black ink, appearing to read "Jingfang Ju".

Jingfang Ju, Ph.D.  
Associate Professor  
Co-Director of Translational Research Lab  
Department of Pathology  
Stony Brook University School of Medicine  
Stony Brook, New York 11794-8691  
Phone: (631)-444-3598 (direct)



Office of the Chair  
Department of Internal Medicine  
3100A Taubman Center  
1500 E. Medical Center Dr.  
Ann Arbor, MI 48109-0368  
(734) 936-4340  
(734) 936-7024 fax

March 5, 2015

Ellen Li, M.D.-Ph.D.  
Director, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

**Re: Feasibility Studies to Build Collaborative Partners in Cancer Research**

Dear Dr. Li:

I am delighted to serve on the External Advisory Board for your proposal entitled '**Partnership to Study Racial/Ethnic Differences in GI Cancer Biology**', which brings together investigators from Stony Brook Medicine with investigators from Downstate Medical center and investigators at the Cold Spring Harbor Laboratories (CSHL) to study health disparities in GI Cancers.

I have >20 years experience in the field of colorectal cancer and genetics within gastroenterology, and know the importance of training the next generation of physician-scientists, with experience as a T32 director, fellowship director, division chief and department chair, coupled with the more than 50 trainees I have mentored. I have a vested interest in the field of cancer disparities, with experience as PI (current U01) and former co-PI of a U54 Comprehensive Cancer Center Partnership, Program Leader of the Reducing Cancer Disparities program at a comprehensive cancer center, and multiple publications regarding the approach to care and the biology of colorectal cancer among African Americans.

I believe that all of the projects proposed in your application will not only have an impact on our understanding of the biological basis for differences in GI cancer incidence and outcomes in underrepresented minorities, but will also lead to the development of more personalized approaches to the treatment of GI cancers, and hopefully progress in the elimination of health disparities in the outcomes of these deadly diseases.

Sincerely,

A handwritten signature in black ink, appearing to read 'John M. Carethers'.

John M. Carethers, M.D., FACP, FACG, AGAF  
John G. Searle Professor and Chair  
Department of Internal Medicine  
University of Michigan



March 19, 2015

Ellen Li, M.D.-Ph.D.  
Director, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

**Re: Feasibility Studies to Build Collaborative Partners in Cancer Research**

Dear Dr. Li:

As a pancreatic cancer researcher, I am delighted to serve on the External Advisory Board for your proposal entitled '**Partnership to Study Racial/Ethnic Differences in GI Cancer Biology**', which brings together investigators from Stony Brook Medicine with investigators from Downstate Medical center and investigators at the Cold Spring Harbor Laboratories (CSHL) to study health disparities in GI Cancers.

The overall focus of my cancer biology research program is to identify and validate the role of novel molecular targets in the development and progression of normal cells transforming into cancer cells of the pancreas. With collaborations in academia and industry, we study At the AACR-Lustgarten Special Conference on Pancreatic Cancer in 2014, I had the pleasure of meeting with Dr. Tuveson and discussing my concern with the health disparity of pancreatic cancer seen with African Americans and other minorities. They have been shown to have a higher incidence rate and a worse prognosis than the majority of the population. I am very interested in better understanding the role biology plays with this health disparity.

I am particularly interested in the pilot P20 grant being submitted by Dr. Gerardo Mackenzie and Dr. Tuveson. They propose to test novel compounds in pancreatic organoids, generated from endoscopic fine needle biopsies from African American and Caucasian patients. This project will generate a living biobank of both resectable and unresectable pancreatic cancers and will increase access of pancreatic cancer researchers such as myself to patient based samples.

I look forward to working together with this team in the future.

Sincerely,

A handwritten signature in cursive script that reads 'Antonio T. Baines'.

Antonio T. Baines, Ph.D.  
Associate Professor  
Department of Biology & Cancer Research Program  
North Carolina Central University

Adjunct Associate Professor  
Department of Pharmacology  
School of Medicine  
UNC-Chapel Hill

March 11, 2015

Ellen Li, MD, PhD  
Director, Division of Gastroenterology and Hepatology  
Stony Brook Medicine  
PO Box 1554, Stony Brook, NY 11790-0988

Re: **Feasibility Studies to Build Collaborative Partners in Cancer Research**

Dear Dr. Li:

I am truly honored to serve on the External Advisory Board for your NIH P20 grant entitled '**Partnership to Study Racial/Ethnic Differences in GI Cancer Biology**', which is a collaborative effort between Stony Brook Medicine, Downstate Medical Center and investigators at the Cold Spring Harbor Laboratories (CSHL).

The Arthur Ashe Institute has a long standing relationship with SUNY Downstate and has a network of community collaborators with similar missions of improving health and access to health care in the inner city population. I have over a decade of experience working with community groups at the Arthur Ashe Institute and also with the Brooklyn Health Disparities Center, where I serve as Director of the Community engagement Core. The Brooklyn Health Disparities Center was created in 2014 as a collaboration between the Arthur Ashe Institute, SUNY Downstate and the Office of the Brooklyn Borough President to address disparities in Brooklyn. I have extensive experience in developing and implementing community based interventions utilizing community based participatory research (CBPR), which will be useful in advising the executive committee of this proposal to enhance the recruitment of minority research subjects into the study. Therefore this application is in alignment with our mission, and I am honored to serve in an advisory capacity if this proposal is funded.

I am also looking forward to discussions and planning towards the annual primary care conference. Best wishes on your application.

Sincerely,



Marilyn Fraser-White, MD  
Deputy Director (AAIUH)  
Director, Community Engagement Core (BHDC)



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*"Start where you are, use what you have, do what you can."*

## Resource Sharing Plan: OVERALL

We will follow relevant NIH guidelines for data sharing. In accordance with NIH Resource Sharing Policy and the NIH Genomic Data Sharing Policy effective January 25, 2015, the investigators will share data and resources at the earliest opportunities throughout this research, subject to patient privacy concerns. Following careful curation of sequence data and clinical metadata, the Steering Committee will review the release of those data to the appropriate NCBI databases (dbGAP, Short Read Archive or SRA). Tables on cohort subject and sample metadata will be deposited in dbGAP, which is a controlled access database. We anticipate that the data generated by the team will be made available as somatic variant data and can therefore be placed on publicly accessible repositories. In addition, results will be written up and sent for publication in relevant journals and the investigators will seek to present publishable results at scientific conferences worldwide.

The Cold Spring Harbor Cancer Center will develop the human pancreatic ductal organoids as a resource for our collaborators at SUNY and the broader research community. We have obtained IRB approval to collect de-identified clinical data and tissue specimens from SUNY. The patients are consented for the research described in this proposal by SUNY Stony Brook, and have agreed to the sequencing of their tissue specimens and the sharing of this de-identified information. We plan to collect 10 to 20 patient derived samples over each year. Each patient-derived organoid will be carefully annotated and stored in liquid nitrogen at early passages. We will build an electronic database to categorize and track established human organoid. Our results will be freely shared with the NCI and the research community through publications and a website. The organoids will be made available to the broader research community, either before or immediately after publication, and will be deposited into a repository/stock center at CSHL, and at SUNY Stony Brook and SUNY Downstate. In addition, we will provide relevant de-identified genetic and phenotypic data obtained from the clinic with the human organoids to the research community. Finally, all sequencing data and other electronic resource will be made available to qualified researchers through the secure database of Genotypes and Phenotypes (dbGAP) web portal.

All training modules with data obtained during evaluation will be made available for use by others at no cost.

## APPLICATION FOR FEDERAL ASSISTANCE

**SF 424 (R&R)****5. APPLICANT INFORMATION****Organizational DUNS\*:** 8048782470000

Legal Name\*: The Research Foundation for SUNY, Stony Brook University  
 Department: Office of Sponsored Programs  
 Division: OVPR  
 Street1\*: STONY BROOK UNIVERSITY  
 Street2: The Office of Sponsered Programs  
 City\*: STONY BROOK  
 County: Suffolk  
 State\*: NY: New York  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 117940000

Person to be contacted on matters involving this application

Prefix: First Name\*: Middle Name: Last Name\*: Suffix:  
 Ms. Andria Adler  
 Position/Title: Grant Administrator  
 Street1\*: W5510 Melville Library  
 Street2: Stony Brook University  
 City\*: Stony Brook  
 County: Suffolk  
 State\*: NY: New York  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 117943362  
 Phone Number\*: 631 632-1610 Fax Number: 631 632-6963 Email: andria.adler@stonybrook.edu

**7. TYPE OF APPLICANT\***

X: Other (specify)

Other (Specify): Non Profit

**Small Business Organization Type**☐ Women Owned☐ Socially and Economically Disadvantaged**11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT\***

Administrative Core

**12. PROPOSED PROJECT**

Start Date\* Ending Date\*  
 09/01/2015 08/31/2019

**Project/Performance Site Location(s)****Project/Performance Site Primary Location**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY, Stony Brook University  
Duns Number: 8048782470000  
Street1\*: STONY BROOK UNIVERSITY  
Street2: The Office of Sponsered Programs  
City\*: STONY BROOK  
County:  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 117940000  
Project/Performance Site Congressional District\*: NY\_001

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**Project/Performance Site Location 1**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY - Downstate Medical Center  
DUNS Number: 0407963280000  
Street1\*: 450 Clarkson Avenue  
Street2:  
City\*: Brooklyn  
County: Kings  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 112030000  
Project/Performance Site Congressional District\*: NY-011

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File Name

**Additional Location(s)**

## RESEARCH &amp; RELATED Other Project Information

<b>1. Are Human Subjects Involved?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
1.a. If YES to Human Subjects Is the Project Exempt from Federal regulations? <input type="radio"/> Yes <input type="radio"/> No If YES, check appropriate exemption number:      — 1   — 2   — 3   — 4   — 5   — 6 If NO, is the IRB review Pending? <input type="radio"/> Yes <input type="radio"/> No IRB Approval Date: Human Subject Assurance Number	
<b>2. Are Vertebrate Animals Used?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
2.a. If YES to Vertebrate Animals Is the IACUC review Pending? <input type="radio"/> Yes <input type="radio"/> No IACUC Approval Date: Animal Welfare Assurance Number	
<b>3. Is proprietary/privileged information included in the application?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
<b>4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
4.b. If yes, please explain: 4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? <input type="radio"/> Yes <input type="radio"/> No 4.d. If yes, please explain:	
<b>5. Is the research performance site designated, or eligible to be designated, as a historic place?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
5.a. If yes, please explain:	
<b>6. Does this project involve activities outside the United States or partnership with international collaborators?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
6.a. If yes, identify countries: 6.b. Optional Explanation:	
<b>7. Project Summary/Abstract*</b>	Filename ADMINabstract_031915FINAL.pdf
<b>8. Project Narrative*</b>	OverallProjectNarrativefinal.pdf
<b>9. Bibliography &amp; References Cited</b>	ADMINISTRATIVECOREREFERENCESSH_L_FINAL.pdf
<b>10. Facilities &amp; Other Resources</b>	
<b>11. Equipment</b>	
<b>12. Other Attachments</b>	Biosketch_Binder1_A.pdf

## ABSTRACT

Two SUNY medical campuses (SUNY Stony Brook and SUNY Downstate) serving underrepresented minority communities with cancer health disparities are partnering with the NCI designated Cancer Center at the Cold Spring Harbor Laboratory (CSHL) to evaluate biological and genetic differences in GI cancers (colorectal and pancreatic) that may link to differences in cancer incidence and outcome observed in racial and ethnic minorities (URM). For the Cancer Research Program, we aim to augment the representation of underrepresented minorities in the collection of biospecimens and linked high dimensional 'omic datasets generated from these biospecimens. In this planning grant we plan to develop a SUNY Downstate GI Biobank that operates in parallel to the SUNY Stony Brook GI BioBank using standard operating procedures. We are planning the development of an integrative biomedical informatics platform that will link the biospecimens with longitudinal clinical data and with the data generated from these specimens. An initial step in the planning procedure is to develop a consensus of what data elements to include and for a controlled vocabulary. To increase community participatory research among racial and ethnic minority populations, we plan to leverage the resources and expertise of the SUNY Downstate Brooklyn Health Disparities Center (led by Dr. Moro Salifu) in developing community education and outreach programs in underserved communities with a high proportion of racial and ethnic minorities. The collection of biospecimens will be driven by two pilot research projects, P1 and P2. In P1, we propose to compare genomic and epigenetic profiling of URM colon cancers with non URM colon cancers. In P2, we propose to test the feasibility of adapting an innovative 3-D method to grow pancreatic organoids (miniature pancreas) from progenitor cells (developed in Dr. Tuveson's laboratory at CSHL) from fine needle core biopsies of human pancreatic cancers collected at the two SUNY medical campuses. We plan to compare genomic and epigenomic profiling of URM pancreatic organoids with those of non-URM organoids. For the Training and Education Program, we are committed to improving the participation of underrepresented minorities in biomedical research and in increasing awareness of health disparities among established cancer researchers. In this planning grant the two SUNY medical campuses will partner with CSHL to create an integrated doctoral certificate program, Scholars in BioMedical Sciences in Cancer Health Disparities. This program is designed to engage doctoral students in translational medicine, particularly in cancer health disparities, by promoting in these students an understanding of the presentation, progression and treatment of diseases related to their area of thesis research. The track requires the addition of a clinical co-mentor to the usual student-basic science advisor team who will help guide the student's biomedical/clinical research and immerse the student in clinical experiences, vocabulary, and the overall culture of clinical research.

## **Project Narrative**

In the US, individuals of African descent are at higher risk for developing GI cancers (colorectal and pancreatic) and also exhibit higher mortality rates for these cancers compared to individuals of Caucasian descent. This grant will serve to build an integrative partnership between two SUNY medical campuses, Stony Brook and Downstate, and the NCI-designated Cancer Center at Cold Spring Harbor Laboratories to study racial and ethnic differences in GI cancer biology. Along with community education and outreach programs, this partnership will improve our ability to collect the under-represented minority (URM) biospecimens that are critical for research addressing the disparity of URM populations and GI cancers. By integrating the education and training resources of these three institutions, we will increase the recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies.

Program Director/Principal Investigator (Last, First, Middle): CARETHERS, John M.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>JOHN M. CARETHERS, M.D.</b>	POSITION TITLE John G. Searle Professor of Internal Medicine Chair, Department of Internal Medicine		
eRA COMMONS USER NAME (credential, e.g., agency login) jcarethers			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Wayne State University	B.S.	1981-1985	Biological Sciences
Wayne State University	M.D.	1985-1989	Medicine
Massachusetts General Hospital	Residency	1989-1992	Internal Medicine
University of Michigan Hospitals	Fellowship	1992-1995	Gastroenterology

**A. Personal Statement**

I have >20 years experience in the field of colorectal cancer and genetics within gastroenterology, and know the importance of training the next generation of physician-scientists, with experience as a T32 director, fellowship director, division chief and department chair, coupled with the more than 50 trainees I have mentored. I have a vested interest in the field of cancer disparities, with experience as PI (current U01) and former co-PI of a U54 Comprehensive Cancer Center Partnership, Program Leader of the Reducing Cancer Disparities program at a comprehensive cancer center, and multiple publications regarding the approach to care and the biology of colorectal cancer among African Americans.

**B. Positions, Employment, and Honors**

1995-2001 Assistant Professor of Medicine in Residence, University of California, San Diego  
 2000-2004 Gastroenterology Fellowship Director, University of California, San Diego  
 2001-2005 Associate Professor of Medicine, University of California, San Diego  
 2002-2005 Chief, Gastroenterology Section, VA San Diego Healthcare System  
 2004-2009 Chief, Division of Gastroenterology, University of California, San Diego  
 2005-2009 Professor of Medicine (tenured), University of California, San Diego  
 2007-2010 Director, UCSD Gastroenterology NIH T32 Training Grant  
 2007-2009 Director, UCSD NIH Digestive Diseases Research Development Center (DDRDC)  
 2008-2009 co-Program Leader, Reducing Cancer Disparities, UCSD Comprehensive Cancer Center  
 2008-2012 co-PI, NCI U54 Comprehensive SDSU/UCSD Cancer Center Partnership  
 11/2009- John G. Searle Professor and Chairman, Dept. of Internal Medicine, University of Michigan

**Other Experience and Professional Memberships**

2000-2003 Editorial Board, *American Journal of Physiology: Gastrointestinal & Liver Physiology*  
 2002-2006 NIH CSR Gastrointestinal Cell and Molecular Biology Study Section (GCMB)  
 2006-2011 Board of Editors, *Gastroenterology*; Section Editor, *This Month in Gastroenterology*  
 2006-2008 National Commission on Digestive Diseases (appointed by Elias Zerhouni, M.D.)  
 2007-2012 AGA Council; Vice-Chair (07-09) and Chair (09-12) of Gastrointestinal Oncology Section  
 2009-2010 AGA Underrepresented Minorities Committee  
 2010-2014 University of Michigan Hospitals and Health Centers Executive Board (elected)  
 2011-2016 Senior Associate Editor, *Gastroenterology*  
 2012-2017 American Association of Physicians (AAP) Councilor (elected)  
 2014-2017 University of Michigan Medical School Executive Committee (elected)

**Honors**

Alpha Omega Alpha Honor Medical Society (1988); Commonwealth Fund Medical Research Fellow, National Medical Fellowships (1988); Henry J. Kaiser Family Foundation Award, National Medical Fellowships (1989); Franklin C. McLean Award, National Medical Fellowships (1989); UCSD Department of Medicine Graduating House Staff Teaching Award (1999); Fellow, American College of Physicians (FACP) (1999); Fellow,

Principal Investigator/Program Director (Last, First, Middle): CARETHERS, John M.

American College of Gastroenterology (FACG) (2001); UCSD Gastroenterology Fellows Excellence in Clinical Teaching Award (2004); Fellow, American Gastroenterological Association (AGAF) (2005); Western Association of Physicians (2006); UCSD School of Medicine Vice-Chancellor's Award for Mentoring Excellence (2006); American Society for Clinical Investigation (2008); American Association of Physicians (2011); Institute of Medicine, National Academy of Sciences (2012); American Clinical and Climatological Association (2014); Wayne State University School of Medicine Distinguished Alumni Award (2015)

### C. Selected peer-reviewed publications (in chronological order, from a total of >110)

1. **Carethers JM**, Hawn MT, Chauhan DP, Luce MC, Marra G, Koi M, Boland CR. Competency in mismatch repair prohibits clonal expansion of cancer cells treated with *N*-methyl-*N*-nitro-*N*-nitrosoguanidine. *J Clin Invest* 1996; **98**:199-206. PMID: 507417.
2. Zigman AF, Lavine JE, Jones MC, Boland CR, **Carethers JM**. Localization of Bannayan-Riley-Ruvalcaba syndrome gene to chromosome 10q23. *Gastroenterology* 1997; **113**:1433-1437. PMID: 9352843
3. **Carethers JM**, Hawn MT, Greenson JK, et al. Prognostic significance of allelic loss at chromosome 18q21 for stage II colorectal cancer. *Gastroenterology* 1998; **114**:1188-1195. PMID: 9609755
4. **Carethers JM**, Furnari FB, Zigman AF, Lavine JE, Jones MC, Graham GE, Teebi AS, Huang H-JS, Ha HT, Chauhan DP, Chang CL, Cavenee WK, Boland CR. Absence of *PTEN/MMAC1* germline mutations in sporadic Bannayan-Riley-Ruvalcaba syndrome. *Cancer Res* 1998; **58**:2724-2726. PMID: 9661881
5. **Carethers JM**, Chauhan DP, Fink D, Nebel S, Bresalier RS, Howell SB, Boland CR. Mismatch repair proficiency and *in vitro* response to 5-fluorouracil. *Gastroenterology* 1999; **117**: 123-131. PMID: 1038191
6. Yashiro M, **Carethers JM**, Laghi L, Saito K, et. al. Genetic pathways in the evolution of morphologically distinct colorectal neoplasms. *Cancer Res* 2001; **60**:2676-2683. PMID: 11289147
7. Huang SC, Lavine JE, Boland PS, Newbury RO, Kolodner R, Pham T-TT, Boland CR, **Carethers JM**. Germline characterization of early-aged onset of hereditary non-polyposis colorectal cancer. *J Pediatr* 2001; **138**:629-635. PMID: 11343035
8. Chang CL, Marra G, Chauhan DP, Ha HT, Chang DK, Ricciardiello L, **Carethers JM**, et. al. Oxidative stress inactivates the DNA mismatch repair system. *Am J Physiol Cell Physiol* 2002; **283**:C148-C154. PMID: 12055083
9. Ashkortab H, Smoot DT, **Carethers JM**, Rahmanian M, Kittles R, Vosgianian G, Doura M, Nidhiry E, Naab T, Momen B, Shakhani S, Giardiello FM. High incidence of microsatellite instability in colorectal cancer from African Americans. *Clinical Cancer Res* 2003; **9**:1112-1117. PMID: 12631615
10. **Carethers JM**, Smith EJ, Behling CA, Nguyen L, Tajima A, Doctolero RT, Cabrera BL, Goel A, Arnold CA, Miyai K, Boland CR. Use of 5-fluorouracil and survival in patients with microsatellite unstable colorectal cancer. *Gastroenterology* 2004; **126**: 394-401. PMID: 14762775
11. Jung B, Doctolero RT, Tajima A, Nguyen AK, Keku T, Sandler RS, **Carethers JM**. Loss of activin receptor type 2 protein expression in microsatellite unstable colorectal cancers. *Gastroenterology* 2004; **126**:654-659. PMID: 14988818
12. Goel A, Arnold CN, Niedzwiecki D, **Carethers JM**, Wasserman L, et al. Frequent inactivation of PTEN by promoter hypermethylation and its association with microsatellite instability-high (MSI-H) in sporadic colorectal cancers. *Cancer Res* 2004; **64**:3014-3021. PMID: 15126336
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14. Satia JA, Keku T, Galanko JA, Martin C, Doctolero RT, Tajima A, Sandler RS, **Carethers JM**. Diet, lifestyle, and genomic instability in the North Carolina Colon Cancer Study. *Cancer, Epidemiol, Biomarkers, and Prevention* 2005; **14**:429-436. PMID: 15734969
15. Ashktorab H, Smoot DT, Farzanmehr H, Fidelia-Lambert M, Momen B, Hyland L, Iacoso-Dononue C, **Carethers JM**, Goel A, Boland CR, Giardiello FM. Clinicopathological features and MSI in colorectal cancers from African Americans. *International Journal of Cancer* 2005; **116**:914-919. PMID: 15856472
16. **Carethers JM**. Unwinding the heterogeneous nature of hamartomatous polyposis syndromes. *JAMA* 2005; **294**:2498-2500. PMID: 16287964
17. Jung B, Smith EJ, Doctolero RT, Gervaz P, Alonso JC, Miyai K, Keku T, Sandler RS, **Carethers JM**. Influence of target gene mutation on survival, stage, and histology in sporadic microsatellite unstable colon cancers. *International Journal of Cancer* 2006; **118**:2509-2513. PMID: 16380996

Principal Investigator/Program Director (Last, First, Middle): CARETHERS, John M.

18. Beck SE, Jung BH, Fiorino A, Gomez J, Del Rosario E, Cabrera BL, Huang SC, Chow JYC, and **Carethers JM**. Bone morphogenetic protein signaling and growth suppression in colon cancer. *Am J Physiology GI & Liver Physiology* 2006; **291**:G135-G145. PMID: 16769811
19. Jung BH, Beck SE, Cabral J, Chau E, Cabrera BL, Fiorino A, Smith EJ, Bocanegra M, **Carethers JM**. *Activin type 2 receptor* restoration in MSI-H colon cancer suppresses growth and enhances migration with activin. *Gastroenterology* 2007; **132**:633-644. PMID: 17258738.
20. Beck SE, Jung B, Del Rosario E, Gomez J, **Carethers JM**. BMP-induced growth suppression in colon cancer cells is mediated by p21/WAF1 stabilization and modulated by RAS/ERK. *Cell Signal* 2007; **19**:1465-1472. PMID: 17317101
21. Beck SE, **Carethers JM**. BMP suppresses *PTEN* expression via RAS/ERK signaling. *Cancer Biol & Ther*, **6**:1313-1317, 2007. PMID: 18059158
22. Chow JYC, Quach KT, Cabrera BL, Cabral JA, Beck SE, **Carethers JM**. RAS/ERK modulates TGF $\beta$ -regulated *PTEN* expression in human pancreatic adenocarcinoma cells. *Carcinogenesis*; **28**:2321-2327, 2007. PMID: 17638924
23. Shin SK, Nagasaka T, Jung BH, Matsubara N, Kim WH, **Carethers JM**, Boland CR, Goel A. Epigenetic and genetic alterations in Netrin-1 receptors UNC5C and DCC in human colon cancer. *Gastroenterology*; **133**:1849-1857, 2007. PMID: 18054557
24. Chow JYC, Dong H, Quach KT, Nguyen PNV, Chen K, **Carethers JM**. TGF $\beta$  mediates *PTEN* suppression and cell motility through calcium-mediated PKC $\alpha$  activation in pancreatic cancer cells. *Am J Physiol Gastrointest Liver Physiol*, **294**:G899-G905, 2008. PMID: 18239055
25. Grady WM and **Carethers JM**. Genomic and epigenetic instability in colorectal cancer pathogenesis. *Gastroenterology* **135**:1079-1099, 2008. PMC2866182.
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27. Chung H, Young DJ, Lopez C, Le T-AT, Lee JK, Ream-Robinson D, Huang SC, **Carethers JM**. Mutation rates of *TGFB2* and *ACVR2* coding microsatellites in human cells with defective DNA mismatch repair. *PLoS ONE* **3**:e3463, 2008. PMC2565065.
28. Jung BH, Gomez J, Chau E, Cabral J, Lee JK, Anselm A, Slowik P, Ream-Robinson D, Messer K, Sporn J, Shin SK, Boland CR, Goel A, **Carethers JM**. Activin signaling in microsatellite stable (MSS) colon cancers is disrupted by a combination of genetic and epigenetic mechanisms. *PLoS ONE*, **4**:e8308, 2009. PMC2789408.
29. Chow JYC, Ban M, Wu HL, Nguyen F, Huang M, Chung H, Dong H, **Carethers JM**. TGF $\beta$  downregulates *PTEN* via activation of NF- $\kappa$ B in Pancreatic Cancer Cells. *Am J Physiol Gastrointest Liver Physiol*, **298**:G275-82, 2010. PMID: 19940030
30. Chung H, Lopez CG, Young DJ, Ream-Robinson D, Cabrera BL, **Carethers JM**. Flanking sequence specificity determines coding microsatellite heteroduplex and mutation rates with defective DNA mismatch repair. *Oncogene* **29**:2172-2180, 2010. PMID: 20140012
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35. Chung H, Chaudhry J, Lopez, CG, **Carethers JM**. Cyclin E and histone H3 are regulated by 5-fluorouracil in a DNA mismatch repair-dependent manner. *Cancer Biol & Ther* **10**:1147-1156, 2010. PMC3230292.

Principal Investigator/Program Director (Last, First, Middle): CARETHERS, John M.

36. Dong H, Shim K-N, Li J, Estrema C, Orneles T, Nguyen F, Liu S, Ramamoorthy S, Ho S, **Carethers JM**, Chow JYC. Molecular mechanisms underlying  $\text{Ca}^{2+}$ -mediated motility of human pancreatic duct cells. 2010. *Am J Physiol Cell Physiol* **299**:C1493-1503, 2010. PMC3006328.
37. Huang SC, Lee JK, Smith EJ, Doctolero R, Tajima A, Beck SE, Weidner N, **Carethers JM**. Evidence for an hMSH3 defect in familial hamartomatous polyps. *Cancer* **117**:492-500, 2011. PMC3005073
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39. Iwaizumi M, Tseng-Rogenski S, **Carethers JM**. DNA mismatch repair proficiency executing 5-fluorouracil cytotoxicity in colorectal cancer cells. *Cancer Biol Ther* **12**:756-764, 2011. PMC3367669
40. Tajima A, Iwaizumi M, Tseng-Rogenski S, Cabrera BL, **Carethers JM**. Both hMutS $\alpha$  and hMutS $\beta$  complexes participate in 5-fluorouracil cytotoxicity. *PLoS ONE*, **6**:e28117, 2011. PMC3229514
41. Lee S-Y, Miyai K, Han HS, Hwang D-Y, Seong MK, Chung H, Jung BH, Devaraj B, McgGuire KL, **Carethers JM**. Microsatellite instability, EMAST, and morphology associations with T cell infiltration in colorectal neoplasia. *Dig Dis Sci*, **57**:72-8, 2012. PMC3245369
42. Chung H, Chaudhry J, Lai JF, Young DJ, **Carethers JM**. Flanking nucleotide specificity for DNA mismatch repair-deficient frameshifts within *Activin Receptor 2 (ACVR2)*. *Mutat Res*, **729**:73-80, 2012. PMC3237829
43. Ayanian JZ and **Carethers JM**. Bridging Behavior and Biology to Reduce Socioeconomic Disparities in Colorectal Cancer Risk. *J Natl Cancer Inst* **104**:1343-1344, 2012. PMCID: pending
44. Tseng-Rogenski S, Chung H, Wilk MB, Zhang S, Iwaizumi M, **Carethers JM**. Oxidative stress induces nuclear-to-cytosol shift of hMSH3, a potential mechanism for EMAST in colorectal cancer cells. *PLoS ONE* **7**:e50616, 2012. PMC3511561
45. Iwaizumi M, Tseng-Rogenski S, **Carethers JM**. Acidic tumor microenvironment downregulates hMLH1 but does not diminish 5-fluorouracil chemosensitivity. *Mutat Res* **747-748**:19-27, 2013. PMC3770844
46. Ashktorab J, Wansley D, Rahi J, Varma S, Shokrani B, Lee E, Daremipouran M, Laiyemo A, Goel A, **Carethers JM**, Brim H. Toward a comprehensive and systemic methylome signature in colorectal cancers. *Epigenetics* **8**:807-815, 2013. PMCID: PMC3883784
47. **Carethers JM**. DNA testing and molecular screening for colon cancer. *Clin Gastroenterol Hepatol* **12**:377-381, 2014. PMCID: PMC4151968
48. **Carethers JM**. Differentiating Lynch-like from Lynch syndrome. *Gastroenterology* **146**:602-604, 2014. PMCID: PMC4134259
49. **Carethers JM**, Murali B, Yang B, Doctolero RT, Tajima A, Basa R, Smith EJ, Lee M, Janke R, Ngo T, Tejeda R, Ji M, Kinseth M, Cabrera BL, Miyai K, Keku TO, Martin CF, Galanko JA, Sandler RS, McGuire KL. Influence of race on microsatellite instability and CD8<sup>+</sup> T cell infiltration in colon cancer. *PLoS ONE* **9**:e100461, 2014. PMCID: PMC4067325
50. **Carethers JM**. Screening for colorectal cancer in African Americans: Determinants and rationale for an earlier age to commence screening. *Dig Dis Sci* 2015. (in press) PMCID: pending
51. Tseng-Rogenski S, Hamaya Y, Choi D, **Carethers JM**. Interleukin 6 alters localization of hMSH3, leading to DNA mismatch repair defects in colorectal cancer cells. *Gastroenterology* 2015. (in press) PMCID: pending

#### D. Research Support ongoing or completed during the last three years

##### R01 DK067287 Carethers (PI)

09/1/05 to 08/31/16

NIH/NIDDK

##### Microsatellite Instability and the DNA Mismatch Repair System

**Major goals:** To determine the role and expression of the DNA mismatch repair protein hMSH3 in preventing mutation of human DNA at microsatellite sequences.

##### U01 CA162147 Carethers (PI)

09/01/12 to 08/31/17

##### Inflammatory Differentiation of Colorectal Cancer among African Americans

**Major goals:** To evaluate the role of mismatch repair dysfunction and immune and cytokine profiles within colorectal cancers from diverse populations.

Principal Investigator/Program Director (Last, First, Middle): Baines, Antonio, T.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Baines, Antonio Thomas</b>	POSITION TITLE Associate Professor of Biology and the Cancer Research Program		
eRA COMMONS USER NAME			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Norfolk State University	B.S.	1995	Biology
University of Arizona	Ph.D.	2001	Pharmacology/ Toxicology
University of North Carolina at Chapel Hill	Postdoc	2006	Pharmacology

**A. Personal Statement**

I have been interested in molecular targeted therapy of pancreatic cancer for almost 8 years since completion of my postdoc studying oncogenic Ras signaling in pancreatic cancer under Dr. Channing Der. The overall focus of our cancer biology research program is to discover novel molecular targets in cancer, especially pancreatic cancer, which can be targeted by potential cancer therapeutics. We want to understand the role of these molecular targets in the development and progression of normal cells transforming into cancer cells of the pancreas. Most recently, we have become interested in molecular targets that are involved in drug resistance of pancreatic cancer to gemcitabine. Also, we have an interest in the health disparity seen with pancreatic cancer. We look forward to investigating the underlying role biology may contribute to the increased incidence and worse prognosis observed in certain populations.

**B. Positions and Honors****Positions and Employment**

2006-	Assistant Professor of Biology & the Cancer Research Program, J. L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, North Carolina
2008-	Adjunct Assistant Professor of Pharmacology, School of Medicine, UNC-Chapel Hill, Chapel Hill, North Carolina
2011-2012	Consultant, Jasco Pharmaceuticals
2013-	Associate Professor of Biology & the Cancer Research Program, J. L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, North Carolina
2013-	Adjunct Associate Professor of Pharmacology, School of Medicine, UNC-Chapel Hill, Chapel Hill, North Carolina

Principal Investigator/Program Director (Last, First, Middle): Baines, Antonio, T.

- 2014- Member, Curriculum in Toxicology, Graduate School, UNC-Chapel Hill, Chapel Hill, North Carolina
- 2014 Consultant, Clarion Healthcare, LLC

**Professional Memberships and Selected Experiences**

- 1997- Society of Toxicology
- 1997- American Association for Cancer Research
- 2011 *Ad Hoc* Reviewer, NIH Molecular and Integrative Signal Transduction (MIST) Study Section
- 2011 Reviewer, European Journal of Cancer
- 2012- HHMI Grant EXROP Study Section
- 2015 *Ad Hoc* Reviewer, NIH Cancer Drug Development and Therapeutics (CDDT) Study Section

**Selected Honors and Presentations**

- 2006 Invited Seminar Speaker, Gastroenterology Division Research Conference, Duke University Medical Center, Durham, NC
- 2007 Invited Seminar Speaker, Department of Pharmacology Seminar Series, UNC-Chapel Hill, Chapel Hill, NC
- 2011 Society of Toxicology-Toxicologists of African Origin (TAO) Mentor/Educator Award
- 2012 American Association for Cancer Research Minority-Serving Institution Faculty Scholar Awardee
- 2012 Invited Seminar Speakers – Department of Pharmacology and Toxicology– School of Medicine, Indiana University, Indianapolis, IN; Department of Environmental and Molecular Toxicology – NC State University, Raleigh, NC
- 2013 Invited Seminar Speaker – Pharmacology and Toxicology Division – University of Missouri-Kansas City, Kansas City, MO
- 2013 Invited Seminar Speaker – Department of Biology – Massachusetts Institute of Technology (MIT), Boston, MA
- 2014 Invited Seminar Speaker - Eppley Cancer Institute, University of Nebraska Medical Center, Omaha, NE
- 2014 Invited Seminar Speaker – Tolero Pharmaceuticals, Lehigh, UT

**C. Selected Publications**

1. Sauer JM, Hooser SB, Badger DA, **Baines AT**, Sipes IG. (1995) Alterations in chemically induced tissue injury related to all-trans retinol pretreatment in rodents. *Drug Metabolism Reviews* 27(1&2):299-323.
2. Sauer JM, Waalkes MP, Hooser SB, **Baines AT**, Kuester RK, Sipes IG. (1997) Tolerance induced by all-trans-retinol to the hepatotoxic effects of cadmium in rats: role of metallothionein expression. *Toxicology and Applied Pharmacology* 143:110-119.
3. **Baines AT**, Holubec H, Basye JL, Thorne P, Bhattacharyya AK, Spallholz J, Shriver B, Cui H, Roe D, Clark LC, Earnest DL, Nelson MA. (2000) The effects of dietary selenomethionine on polyamines and azoxymethane-induced aberrant crypts. *Cancer Letters* 160:193-198.
4. Lim, K.-H., **Baines, A.T.**, Fiordalisi, J.J., Shipitsin, M., Feig, L.A., Cox, A.D., Der, C.J., and Counter, C.M.: (2005) Activation of RalA is critical for Ras-induced tumorigenesis of human cells. *Cancer Cell* 7:533-545. [PMC15950903]

Principal Investigator/Program Director (Last, First, Middle): Baines, Antonio, T.

5. **Baines, A.T.**, Lim, K.-H., Shields, J.M., Lambert, J.M., Counter, C.M., Der, C.J., and Cox, A.D.: Use of retrovirus expression of interfering RNA to determine the contribution of activated K-Ras and Ras effector expression in human tumor cell growth. Methods in Enzymology. Vol. 407, pp. 556-74, 2005.
6. Xu, D., Allsop, S.A., Witherspoon, S.M., Snider, J.L., Yeh, J.J., Fiordalisi, J.J., White, C.D., Williams, D., and **Baines, A.T.**: (2011) The oncogenic kinase Pim-1 is modulated by K-Ras signaling and mediates transformed growth and radioresistance in human pancreatic ductal adenocarcinoma cells. *Carcinogenesis*, 32(4):488-95. [PMC3066419]
7. **Baines, A.T.**, Xu, D., and Der, C.J.: Inhibition of Ras for cancer treatment: the search continues. Future Medicinal Chemistry, 1787-1808, 2011.
8. Xu, D., Cobb, M., Gavilano, L., Sam Witherspoon, S.M., Williams, D., White, C.D., Taverna, P., Bednarski, B., Hong Kim, H.J., Baldwin, A., and **Baines, A.T.**: (2013) Inhibition of oncogenic Pim-3 kinase modulates transformed growth and chemosensitizes pancreatic cancer cells to gemcitabine. *Cancer Biology & Therapy*, 14:6, 1-10. [PMC3813565]

#### D. Selected Research Support

NCCU/UNC-Lineberger U54 Partnership in Cancer Research Grant-NCI 08/2013-08/2015  
 "Identification of the Pim kinome in pancreatic cancer"  
 Role: Co-Investigator

Jasco Pharmaceuticals Collaborative Grant, "Pim kinase inhibitors in pancreatic cancer"  
 01/11-07/12  
 Role: PI

Duke-NCCU STEM Partnership Grant, "The role of Pim-1 kinase as a novel molecular target in pancreatic cancer" 09/01/08-11/30/09  
 Role: Co-Investigator

NCI/NIGMS MBRS Support of Competitive Research (SCORE) Pilot Project Award (SC2), entitled "The role of Pim kinases as a novel molecular target in pancreatic cancer" 08/01/08-07/31/12  
 Role: PI

Academy of Applied Science and the Army Research Office; Support high school students conducting research during the summers 2008-  
 Role: Co-Investigator

NCCU-BBRI/UNC-Lineberger Partnership in Cancer Research Pilot Grant, "Molecular targets in pancreatic cancer" 10/14/06-04/30/08  
 Role: Co-Investigator

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Fraser- White, Marilyn</b>	POSITION TITLE <b>Deputy Director</b>		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>Mwhite30</b>			
EDUCATION/TRAINING ( <i>Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.</i> )			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
City University of New York at Brooklyn College	BA	02/94	Chemistry
Spartan Health Sciences University School of Medicine	MD	04/00	Medicine

### A. Personal Statement

My experience in conducting community based research, as part of a community-based organization (Arthur Ashe Institute for Urban Health) with long-standing relationships within the community, as well as my leadership roles in the Brooklyn Health Disparities Center will be important to my role in an advisory capacity. In addition to my role as the Deputy Executive Director for the Arthur Ashe Institute, I serve as the Director of the Community Engagement Core of the NIH-NIMHD funded Brooklyn Health Disparities Center, a partnership between the SUNY Downstate Medical Center, the Arthur Ashe Institute for Urban Health, and the Office of the Brooklyn Borough President. In this capacity, my responsibilities include coordinating and supervising the development and implementation of a health disparities curriculum for high school students as well as a curriculum for community leaders to increase their capacity to conduct research. As part of a team of researchers working on a CDC funded project to develop a barbershop based HIV/AIDS risk reduction intervention for African American men, I have supervised the recruitment and formative phase of the project, and have collaborated with other investigators to develop the training modules for the intervention. I have also served as the principal investigator for a grant, funded by the New York University – Clinical & Translational Science Institute, to develop and pilot a cardiovascular disease (CVD) risk reduction intervention to train salon stylists to deliver heart health messages, including stress reduction messages, to their customers. I have coordinated many of the Institute's outreach programs, including the federally funded programs, and was instrumental in developing the Institute's salon and barbershop based programs into behavioral health intervention models. I have also served as a co-investigator for the Institute's ACCESS program to increase access to health and social resources for formerly incarcerated individuals and their families. As an NIH LRP award recipient, I conducted preliminary work to assess CVD risk factors among formerly incarcerated Black men. Additionally, I served as part of an investigative team of researchers to develop training curricula on various topics including cardiovascular disease, cancer (breast, prostate and colorectal), diabetes, HIV/AIDS, health disparities and community based participatory research. Most recently, I was the recipient of the Fulbright Research Specialist award. Given my vast experience in developing and conducting community health disparities intervention programs and leading the community engagement efforts of the Institute and the Brooklyn Health Disparities Center, I am well prepared to serve as a member of the advisory board.

### B. Positions and Honors.

#### Positions and Employment

1994-1996	<i>Public Health Advisor</i> , New York City Department of Health, Bureau of Tuberculosis Control (Regulatory Affairs), New York, NY,
2000-2001	<i>Outreach Coordinator/ Program Director (Acting)</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2001-2004	<i>Research Manager</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2003-present	<i>Instructor</i> , Health Science Academy (Arthur Ashe Institute)
2004-2012	<i>Associate Director, Research &amp; Training</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2007	<i>Acting Deputy Director</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2012-present	<i>Deputy Director</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY

## **Awards/ Honors**

Steven Biko Memorial Scholarship (1988)  
 Minority Access to Research Careers (MARC) Fellowship (1988-1990)  
 Sigma-Xi Rudin Fellowship Award (1990)  
 SIPID Scholar (2008)  
 Project Interchange Alumni (2008)  
 Health Award (New York State Association of Black & Puerto Rican Legislators, Inc.) (2011)  
 Extraordinary Women of Downstate Award (2012)  
 NIH Loan Repayment Program award recipient (2012-2014)  
 New York State Department of Health – Commissioner’s Special Recognition Award (2013)  
 Fulbright Research Specialist Fellowship Award (2013)  
 Innovator Award – Bedford Stuyvesant Family Health Center (2014)

## **C. Contribution of Science**

### **1. Development of Culturally Tailored Interventions**

I have worked closely with members of the community and faculty at various institutions to develop and implement culturally tailored curricula on various health issues such as prostate cancer, HIV/AIDS and cardiovascular disease.

- a. Brown N, Naiman P, Homel P, Fraser-White M, Clare R, Browne R. (2006). Assessment of preventive health knowledge and behaviors of African-American and Afro-Caribbean women in urban settings. *J Natl Med Assoc.*, 98(10), 1644-1651. PMID: PMC2569737
- b. Fraser M, Brown H, Homel P, Macchia RJ, LaRosa J, Clare R, Davis-King D, Collins P, Samuel T, Macalino G, Browne R. (2009) Barbers as Lay Health Advocates – Developing a Prostate Cancer Curriculum. *J Natl Med Assoc.*, 101(7), 690-697. PMID: 19634590
- c. Brown, N., Vaughn, N.A., Lin, A.J., Browne, R., White, M., & Smith, P. (2011) Healthy Families Brooklyn: Working with Health Advocates to Develop a Health Promotion Program for Residents Living in New York City Housing Authority Developments. *J. Community Health*, 36(5), 864-873. PMID: 21400120
- d. Boutin-Foster C, George K, Samuel T, Fraser-White M, Brown H. (2008). Training Community Health Workers to be Advocates for Health Promotion: Efforts Taken by a Community-Based Organization to Reduce Health Disparities in Cardiovascular Disease. *Journal of Community Health*, 33(2), 61-68. PMID:18058210

### **2. Replication of Innovative Science Models**

As part of an investigative team of researchers, I have worked on the replication of the Institute’s community outreach efforts in non-traditional settings. As a recipient of a Fulbright Research Specialist award, I developed and implemented a program on climate change and public health in collaboration with the University of the West Indies. I am currently working as a co-investigator on a pilot project across universities in the West Indies and various State Universities of New York to assess cardiovascular disease risk in individuals of Caribbean descent in New York and those in their native Caribbean countries.

- a. Browne R, Vaughn NA, Siddiqui N, Brown N, Delmoor E, Randleman P, Randleman S, Gonzalez L, Lewis J, Lourie R, Foster G, Brown H, Fraser-White M, Banks S. (2009) Community-Academic Partnerships: Lessons Learned from Replicating a Salon-Based Health Education and Promotion Program. *Progress in Community Health Partnerships: Research, Education and Action*, 3(3), 241-248. PMID: 2020822
- b. Henry KR, Fraser-White M, Roberts CR, Wilson TE, Morgan R, Brown H, Shaw R, Jean-Louis G, Graham YJ, Brown C, Browne R. (2012) Engaging Minority High School Students as Health Disparities Interns: Findings and Policy Implications of a Summer Youth Pipeline Program. *J Natl Med Assoc.*, 104 (9, 10), 412-419

### **3. Community Engaged Research**

One of my contributions to science has been my extensive work in the community, in developing, implementing and assessing interventions that are focused on addressing health disparities and reducing risk factors for disease.

- a. Clark, L, Browne, R., Kokolis, R., White, M., Morales, S.: Health Disparities and Cardiovascular Disease, in Clark, LT (ed.): Cardiovascular Disease and Diabetes: Modern Management. New York, McGraw-Hill, 2006; p 506
- b. Wilson T, Fraser-White M, Feldman J, Homel P, Wright S, King G, Coll B, Banks S, Davis-King D, Price M, Browne R. (2008). Hair salon stylists as breast cancer prevention lay health advisors for African American and Afro-Caribbean women. Journal of Health Care for the Poor and Underserved, 19, 216-226. PMID:18263997
- c. Wilson TE, Fraser-White M, Williams KM, Pinto A, Agbetor F, Camilien B, Henny K, Browne RC, Gousse Y, Taylor TN, Brown H, Taylor RD, Joseph MA. Barbershop Talk with Brothers: Using Community-Based Participatory Research to Develop and Pilot Test a Program to Reduce HIV Risk among Black Heterosexual Men. AIDS Educ Prev 2014 Oct;26(5):383-97
- d. Taylor TN, Joseph MA, Henny KD, Pinto AR, Agbetor F, Camilien B, Williams KM, Browne RC, White M, Gousse Y, Brown H, Taylor RD, Wilson TE. Perceptions of HIV risk and explanations of sexual risk behavior offered by heterosexual Black male barbershop patrons in Brooklyn, NY. Journal of Health Disparities Research and Practice [forthcoming].

#### 4. Community Based Participatory Research (CBPR)

The importance of fostering community-academic partnerships is essential to the success of research efforts that are focused on eliminating health disparities. I have had the opportunity to develop and implement training activities for community based organizations and faculty on CBPR. I have worked closely with CBO's on increasing the capacity of community numbers to conduct research

- a. Roberts CB, Browne R, Wilson TE, Morgan R, Brown H, Shaw R, Jean-Louis G, Brown C, Fraser-White M. Lessons Learned from Building an Infrastructure for Community-Based Participatory Research. International Public Health Journal [in press]
- b. Henry KR, Fraser-White M, Roberts CR, Wilson TE, Morgan R, Brown H, Shaw R, Jean-Louis G, Graham YJ, Brown C, Browne R. (2012) Engaging Minority High School Students as Health Disparities Interns: Findings and Policy Implications of a Summer Youth Pipeline Program. J Natl Med Assoc., 104 (9, 10), 412-419

### 5. Research Support

#### Ongoing Research Support

HHSN276201400887P

National Library of Medicine Fraser-White (PI)

09/30/14 – 09/29/15

"AAIUH mHealth HIV/AIDS Risk Reduction Initiative"

The goal of the project is to facilitate and improve access to NLM's HIV/AIDS medical information and educational resources for high-need individuals, caregivers, family, friends and other community members.

Role: Director

P1-12-001

Jensen, Levine (PIs)

07/01/12 – 06/30/14

PCORI

"Mobile Apps (MAPPS): Patient & Caregiver Attitudes, Behaviors & Knowledge"

The aim of this collaborative project is to explore the needs, attitudes, knowledge, and behavior toward M-tech for health management within the model of stroke, as stroke survivors and their caregivers require continuous monitoring and informational updates.

Role: Co-investigator

1P20MD006875-01

Browne, Salifu (PIs)

06/14/12 – 01/31/17

NIH - NIMHD

"Brooklyn Health Disparities Center – Community Engagement"

The goal of this grant is to strengthen the capacity of the Brooklyn Health Disparities Center through its community engagement core by developing and implementing a health disparities curriculum for high school students and a curriculum on community based participatory research to increase the capacity of local community based organizations.

Role: Director – Community Engagement

NIH-Loan Repayment Program (LRP) Fraser-White (PI) 2012-2014

“ACCESS Project for Formerly Incarcerated Individuals”

The goal of this grant is to assess cardiovascular disease risk factors among formerly incarcerated individuals.

Role: Loan Repayment Program Participant

### **Completed Research Support**

New York Department of Health

03/15/12-07/15/12

*Communities of Color Condom Distribution Project*

The goal of this project is to raise awareness about HIV/AIDS among minorities, through distribution of condoms and information on HIV/AIDS (i.e. brochures, pamphlets and video documentary), in non-traditional venues such as barbershops and salons in Central Brooklyn.

Role: Director

1UL1RR029893

White (PI)

03/29/10-03/28/11

NYU-HHC CTSI

*“Heart of a Woman”*

The goal of this grant is to pilot a cardiovascular disease curriculum to train community- based professional stylists, as messengers, to deliver heart health messages to their customers to promote healthy behaviors that will reduce risk of cardiovascular disease in minority women.

Role: Principal Investigator

1P20MD005092-01

Brown, Browne, Wilson (PIs)

09/30/09 – 07/31/12

NIH - NCMHD

*“Brooklyn Health Disparities Center – Community Engagement”*

The goal of this grant is to strengthen the capacity of the Brooklyn Health Disparities Center through its community engagement core by developing and implementing a health disparities curriculum for high school students and a curriculum on community based participatory research to increase the capacity of local community based organizations.

Role: Director – Community Engagement

1 UR6 PS000691-01,  
CDC

Wilson (PI)

09/01/07 – 02/29/12

*“Reducing HIV Heterosexual Risk among African-American Men”*

The overall goal of this project is to develop a program that will reach heterosexual men in barbershops serving communities with high HIV morbidity and AIDS related mortality;

Role: Co-Investigator

Empire BlueCross BlueShield

Browne (PI)

01/01/11-12/31/11

*“Heart of a Woman”*

The goal of this grant is to implement a cardiovascular disease intervention program in which professional salon stylists are trained to deliver heart health messages to their customers to promote healthy behaviors that will reduce risk of cardiovascular disease in minority women.

Role: Co-Investigator

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Samuel Ryu M.D.</b>		POSITION TITLE <b>Professor &amp; Chair, Dept of Radiation Oncology</b>	
eRA COMMONS USER NAME (credential, e.g., agency login) <b>Saryu1</b>			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Kyungpook University School of Medicine, Korea	M.D.	1982	Medicine
Kyungpook University Graduate School, Korea	M.S.	1988	Radiology
Yonsei and Kyungpook University Hospital, Korea	Residency	1986-1989	Radiation Oncology
Henry Ford Hospital, Detroit, MI	Post-doc	1991-1993	Tumor and Radiation Biology
Henry Ford Hospital, Detroit, MI	Residency	1993-1996	Radiation Oncology

**A. Personal Statement:**

As Chair of the Department of Radiation Oncology, I have a strong commitment to the diagnosis, treatment and research of GI cancers. In fact our department is launching a new clinical protocol for treating unresectable/borderline resectable pancreatic adenocarcinoma with SBRT/chemotherapy. My department is consequently very interested in the development of pancreatic organoids from EUS-FNB biopsies, which may serve as a model for assessing the most effective therapy for individual cases of pancreatic cancer.

**B. Positions and Honors:**

1989-1993	Assistant Professor, Radiation Oncology, Kyungpook University Hospital, Korea
1996-1999	Assistant Professor of Radiation Oncology, Upstate Medical Center, Syracuse, NY
1999-2014	Senior Staff, Radiation Oncology, Henry Ford Hospital, Detroit, Michigan
2000-2014	Director, Center for Radiosurgery, Henry Ford Hospital
2005-2014	Leader, Neuro and Spine Oncology/ Spine Tumor Board, Henry Ford Health System
2010-2011	NCI Study Section, Clinical Studies Special Emphasis Panel
2010-	Founding Editor-in-chief, Journal of Radiosurgery and SBRT
2013-2015	President, International Stereotactic Radiosurgery Society
2014-	Professor and Chair, Radiation Oncology, Stony Brook University School of Medicine
2014-	Deputy Director for Clinical Affairs, Stony Brook Cancer Center

**C. Peer-reviewed Publications: (selected)**

- Kleinberg L, Supko JG, Mikkelsen T, Blakeley JO, Stevens G, Ye X, Desideri S, **Ryu S**, Desai B, Giranda VL, Grossman SA. Phase I adult brain tumor consortium (ABTC) trial of ABT-888 (veliparib), temozolomide (TMZ), and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM) including pharmacokinetic (PK) data. *Journal of Clinical Oncology*. 2013;31(15).
- Kim EY, Yechieli RL, Kim JK, Mikkelsen T, Kalkanis S, Rock JP, **Ryu S**. Patterns of Failure after Radiosurgery to different target volumes of enhancing lesion only versus enhancing lesion and FLAIR abnormality for recurrent Glioblastoma Multiforme. *Journal of Neuro-oncology* 116:291-297. 2014 doi: 10.1007/s11060-013-1290-1294. Epub 2013 Oct 31. PMID: 24173682
- Ryu S**, Ryken T, Olson J, Kalkanis S. The role of radiotherapy in the management of progressive glioblastoma multiforme. *Journal of Neuro-oncology* 18(3):489-99, 2014. doi: 10.1007/s11060-013-1337-6. Epub 2014 Apr 12.
- Zhao B, Jin JY, Wen N, Huang Y, Siddiqui MS, Chetty I, **Ryu S**. Prescription to 50-75% isodose line may be

Program Director/Principal Investigator (Last, First, Middle):

- optimum for linear accelerator based radiosurgery of cranial lesions. *Journal of Radiosurgery and SBRT* 2014
5. Jin JY, Huang Y, Brown SL, Movsas M, Chetty IJ, **Ryu S**, Kong FM. Radiation dose-fractionation effects in spinal cord: comparison of animal and human data. *Physics in Medicine and Biology* 2014 (in print)
  6. Huang Y, Chin K, Robbins J, Kim J, Li, H, Amro H, Chetty IJ, Gordon J, **Ryu S**. Radiosurgery of multiple brain metastases with single-isocenter dynamic conformal arcs (SIDCA). *Radiotherapy and Oncology* 112(1):128-32, 2014. doi: 10.1016/j.radonc.2014.05.009. Epub 2014 Jul 2
  7. Chin K, Ryu S. The Use of Jaw Tracking in Intensity Modulated and Volumetric Modulated Arc Radiotherapy for Spine Stereotactic Radiosurgery. *Practical Radiation Oncology* 2014 PRACTICALRADONC-D-14-00138R1
  8. Bellon M, Siddiqui MS, Ryu S, Chetty I. The effect of longitudinal CT resolution and pixel size (FOV) on target delineation and treatment planning in stereotactic radiosurgery. *Journal of Radiosurgery and SBRT* 2014
  9. Robbins JR, Kim SR, Kalkanis S, Cogan C, Rock J, Rosenblum M, Kim JH, **Ryu S**. Stereotactic radiosurgery in the multidisciplinary management of large (target volume  $\geq 20$  cc or  $\geq 3$  cm in diameter) brain metastases. *Journal of Neurosurgery* 2014
  10. Fisher BJ, Hu C, Macdonald DR, Lesser GJ, Coons S, Brachman DG, **Ryu S**, Werner-Wasik M, Bahary JP, Liu J, Chakravati A, Mehta MP. Phase II study of a Temozolomide-based chemoradiotherapy regimen for high-risk low-grade gliomas: Results of RTOG 0424. *International Journal of Radiation Oncology Biology Physics* 91(3): 497-504, 2015
  11. Lo SS, Ryu S, Chang EL, Galanopoulos N, Jones J, Kim EY, Kubicky CD, Lee CP, Rose PS, Sahgal A, Sloan AE, The BS, Traughber BJ, Poznak CV, Vassil, AD. American College of Radiology ACR Appropriateness Criteria® Expert Panel on Radiation Oncology–Bone Metastases: Metastatic epidural spinal cord compression and recurrent spinal metastasis. *Journal of Palliative Medicine* 2015 (in Print)
  12. Thibault I, Lo SS, Chang EL, Sheehan J, Ahluwalia MS, Guckenberger M, Sohn MJ, Ryu S, Foote M, Muacevic A, Soltys SG, Chao S, Gerszten P, Lis E, Yu E, Bilsky M, Fisher C, Schiff D, Fehlings MG, Ma L, Chang S, Chow E, Parelukar W, Vogelbaum M. Challenges Determining Response after Stereotactic Body Radiotherapy for Spinal Metastases and Review of Current Practices: Part 1 of a First Report from the Spine Response Assessment in Neuro-Oncology (SPANO) Group. *Lancet Oncology* 2015 (under review)
  13. Redmond KJ, Robertson S, Lo SS, Soltys S, **Ryu S**, McNutt T, Chao S, Barani I, Yamada J, Ghia A, Chang EL, Sheehan J, Sahgal A. Consensus Contouring Guidelines for Post-Operative Spine Stereotactic Body Radiation Therapy. *ISRS* 2015
  14. **Ryu S**, Yoon H, Stessin A, Rosiello A, Gutman F, Davis R. Contemporary Treatment with Radiosurgery for Spine Metastasis and Spinal Cord Compression in 2015. *Radiation Oncology Journal* 2015 (in print)

## D Research Support

### ACTIVE

2009- RTOG-0631 Phase II/III study of spine radiosurgery for localized spine metastasis. (Role: National P.I. and Study chair) -- U10 CA 21661-325 (RTOG), U10 CA37422-21 (CCOP)

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Minsig Choi MD</b>	POSITION TITLE <b>Associate Professor of Medicine</b>		
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of the Philippines, Metro Manila, Philippines	BS	4/1994	Molecular Biology
Far Eastern University Manila, Philippines	MD	4/1998	Medicine
Chicago Medical School, Chicago, IL	residency	6/2003	Internal Medicine
Wayne State University, Detroit, MI	fellowship	6/2006	Hematology-Oncology

**A. Personal Statement**

I have been actively engaged in clinical and translational research in the field of gastrointestinal cancer with focus in geriatric population and their comorbidities. My research also involves close collaborations with basic researchers other medical disciplines including psychological issues. The major philosophy of my work is that the translational empiric approach in developing new treatments in this disease must be changed to a biology-driven approach. My interests include targeting signaling pathways, immunotherapy and supportive care that involves multidisciplinary approach to cancer care.

**PROFESSIONAL EXPERIENCE**

8/2014 to present Associate Professor in Department of Medicine, Stony Brook University  
Director of Outpatient Oncology

9/2010- 8/2014 Assistant Professor, in Oncology, Karmanos Cancer Institute, NCI-designated Comprehensive Cancer Center and Wayne State University, Detroit, MI

7/2006 to 9/2010, Staff Physician; G. V. Montgomery VA Medical Center Jackson, MS  
Assistant Professor, University of Mississippi, Department of Medicine, Division of Oncology

**MEMBERSHIP**

2010 to 2014 Member/ vice chair of the Phase I Institutional Review Board at Wayne State University  
2006 to 2014 Member of Southwest Oncology Group(SWOG), GI subcommittee  
2003 to present Member of American Society of Clinical Oncology (ASCO)  
2007 to 2010 Member of the Jackson VAMC Institutional Review Board  
2003-2006 served Quality Assurance Committee at Karmanos Cancer Institute/Wayne State University

Board Certification:

Program Director/Principal Investigator (Last, First, Middle):

2007- Board certified in Hematology, American Board of Internal Medicine  
 2006- Board certified in Medical Oncology, American Board of Internal Medicine  
 2003- 2013 Board certified in Internal Medicine, American Board of Internal Medicine

## HONORS/Awards

2012 WSU School of Medicine – College Teaching Award  
 2009 Travel grant from International Society of GI oncology  
 2007 Mississippi Research, “Young Investigator Award”  
 2006 Merit Award form American Society of Clinical Oncology  
 2005 Fellowship travel grant for ASCO  
 1998 cum laude for Doctor of Medicine  
 1998 Most Outstanding Medical Student Award  
 1994 cum laude for BS Molecular Biology  
 1994 Phi Kappa Phi Honor Society

## C. Selected Peer-reviewed Publications

1. Fujiki M, Aucejo F, **Choi M**, Kim R., Neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: where do we stand? *World J Gastroenterol*. 2014 May 14;20(18):5308-19.
2. **Choi M**, Kim R, Saif MW. Is there a role for 2<sup>nd</sup> line chemotherapy in pancreatic cancer? *Journal of Pancreas* 2014 Mar 10;15(2):106-9
3. Yano H, Thakur A., **Choi M**, et. al. Ipilimumab augments antitumor activity of bispecific antibody-armed activated T cells derived from colorectal and pancreatic cancer patients. *Journal of Translational Medicine*, 2014 Jul 9;12:191
4. Al-Hajeli M, Asfar A, **Choi M**. Nab-paclitaxel: potential for the treatment of advanced pancreatic cancer. *Oncotarget and Therapy*, 2014 7:1-6.
5. Salem M, Jain N, Dyson G, **Choi M**, Shields AF, Critchfield J, Philip PA. Radiographic parameters in predicting outcome of patients with hepatocellular carcinoma treated with yttrium-90 microsphere radioembolization. *ISRN Oncology*, 2013 Sep 15;2013:538376. doi: 10.1155/2013/538376;PMID 24167742
6. Kim R, Mahipal A, **Choi M**, Saif MW. Biomarkers for pancreatic cancer: Is it ready for primetime? *Journal of Pancreas*, 2013 Jul 10;14(4):309-11. DOI: 10.6092/1590-8577/1676.
7. Tait L, Meyer J, McSpadden E, Cheng J, Baciewicz F, Meropol N, Cohen S, Wozniak A, **Choi M**, Konski A. Women at increased risk for cardiac toxicity following chemoradiation therapy for esophageal carcinoma. *Practical Radiation Oncology*, Oct 2013, Vol 3, Issue 4, Pages e149-e155.
8. Kim R, Tan A, **Choi M**, El-Rayes B. Geographic Differences in Approach To Advanced Gastric Cancer: Is There A Standard Approach? *Crit Rev Oncol Hematol*. 2013 Jun, 1040-8428(13)101-7.
9. Bang H, Littrup P, Currier B, Goodrich D, **Choi M**, Heilbrun L, Goodman A. Percutaneous Cryoablation of Metastatic Lesions from Colorectal Cancer: Efficacy and Feasibility with Survival and Cost-Effectiveness Observations. *ISRN Minimally Invasive Surgery*. 2012 Sept, Volume 2012, Article ID 942364. DOI: 10.5402/2012/942364.

Program Director/Principal Investigator (Last, First, Middle):

10. **Choi M**, Razzaque S, Kim R. Systemic Therapy of Advanced Pancreatic Cancer: Has the Landscape Changed? Clin Adv Hematol Oncol. 2012 Jul;10(7):442-51. PMID: 23262631
11. Azmi A, Banerjee S, Ali S, Wang Z, Bao B, Beck F, Maitah M, **Choi M**, Shields T, Philip P, Sarkar F, Mohammad R. Network Modeling of MDM2 inhibitor-Oxaliplatin Combination Reveals Biological Synergy in wt-p53 solid tumors. Oncotarget. 2011 May;2(5):378-392.
12. **Choi M**, Craft B, Geraci S. Surveillance and monitoring of adult cancer survivors. American Journal of Medicine. 124(7):598-601, 2011.
13. **Choi M.**, L. Heilbrun, R. Venkatramanamoorthy, Lawhorn-Crews JM, Zalupski MM, Shields AF. Using <sup>18</sup>F Fluorodeoxyglucose Positron Emission Tomography to Monitor Clinical Outcome in Patients Treated with Neoadjuvant Chemo-Radiotherapy for Locally Advanced Pancreatic Cancer. American Journal of Clinical Oncology. 2010 Jun;33(3):257-61.
14. Banerjee S, **Choi M**, Aboukameel Wang Z, Mohammad M, Chen J, Yang D, Sarkar FH, Mohammad RM. Preclinical studies of Apogossypolone, a novel pan inhibitor of Bcl-2 and Mcl-1 synergistically potentiates cytotoxic effect of gemcitabine in pancreatic cancer. Pancreas. 2010 Apr;39(3):323-31.
15. **M. Choi**, P. Jiang, L. Heilbrun, D. Smith, S. Gadgeel. Retrospective review of cancer patients age >80 years old treated with chemotherapy at a comprehensive cancer center. Critical Reviews in Oncology and Hematology. 2008 Sep;67(3):268-72.

#### D. Research Support

Merck (Investigator Initiated), "Prevention of Nausea and Vomiting Secondary to FOLFIRINOX Chemotherapy in GI Cancer Patients", \$62,648 (5/22/12 – present)

Xbiotech USA Inc : 2012-PT023 : 2013-014 : A Pivotal Phase III Study to Evaluate Overall Survival using MABp1 as a Monotherapy in Metastatic Colorectal Cancer Patients with Cachexia, \$ 44,434 (4/9/2013 – 8/2014)

Weill Cornell Medical College : 1208012946 : 2013-035 : An Open-Labeled, Multicenter Phase II Study of Cabazitaxel in Refractory Metastatic Gastric or Gastroesophageal Adenocarcinoma, \$45,000 (7/8/2013-8/2014)

Nordion, Inc., "A Phase III Clinical Trial Evaluating TheraSphere in Patients with Metastatic Colorectal Carcinoma of the Liver who have Failed First Line Chemotherapy", \$40,693 (5/22/12 – 5/21/15)

Nordion, Inc., "A Phase III Clinical Trial of Intra-arterial TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (HCC)", \$27,540 (6/21/12 – 6/20/15)

Myriad Genetics, Inc., "A Prospective, Randomized, Open-Label Trial Comparing OnDose® AUC Optimized 5-FU Based Administration versus Standard Body Surface Area (BSA) Dosing in Metastatic Colorectal Cancer Patients (mCRC) Treated with mFOLFOX6", \$44,467 (7/10/12 – 7/9/13)

Genentech, "A Phase II, Multicenter, Open-Label, Randomized Study Evaluating the Efficacy and Safety of FOLFIRI + MEHD7945A versus FOLFIRI + Cetuximab in Second Line in Patients with KRAS Wild-Type Metastatic Colorectal Cancer", \$189,659 (7/18/12 – 7/1/15)

Program Director/Principal Investigator (Last, First, Middle):

Kyowa Hakko Kirin Pharma, Inc., "Phase I/II Study of KRN330 plus Irinotecan after First-Line or Adjuvant FOLFOX/CapOx Failure in Patients with Metastatic Colorectal Cancer", \$125,152 (4/15/11 – 4/14/14)

Oncothyreon, Inc., "Phase 1/2 Study of PX-866 and Cetuximab", \$ 164,539 (10/11/11 – 10/10/2013)

Abbott Laboratories, "An Open-Label, Randomized Phase 3 Study of the Efficacy and Tolerability of Linifanib (ABT-869) vs Sorafenib in Subjects with Advanced Hepatocellular Carcinoma (HCC) (M10-963)", \$82,150 (2010 – 2011)

KCI, Immunotherapy Treatment of Advanced Colorectal and Pancreatic Cancer with anti-CD3 x anti-Erbitux Armed Activated T Cells (Phase Ib). Role: PI. \$60,000 10/8/11- 8/ 2014

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Styliani-Anna (Stella) E. Tsirka	POSITION TITLE Professor of Pharmacological Sciences		
eRA COMMONS USER NAME (credential, e.g., agency login) stsirka			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Aristotle Univ of Thessaloniki, Greece	BSc	10/84	Chemistry
Aristotle Univ of Thessaloniki, Greece	PhD	01/89	Biochemistry

**A. Personal statement.** My laboratory explores the interactions and communications between the nervous and immune systems in physiological and pathological settings, such as glioma, stroke, epilepsy, multiple sclerosis. Many students and postdocs have worked over the years in these projects. I have been a member of the Molecular and Cellular Pharmacology (MCP/HBH) graduate program since 1998. Between 2003 and 2014 I served as the Director of the MCP/HBH Program. I have trained many graduate students in the Program as dissertation supervisor, and have served in numerous research advisory committees for students. I have mentored four MSTP students and serve on the committees of several others. Since the beginning of 2013 I also put together and direct the Stony Brook University Scholars in BioMedical Sciences program, which is based on the concepts of the HHMI Med-into-Grad programs, facilitating the exposure of graduate students in Life Sciences programs to translational clinical and medical science. I have also mentored several postdoctoral fellows and research scientists who have moved on to successful academic careers. My research has been funded by NIH and other funding sources. I have also been organizing and participating in ethics training for the MCP/HBH graduate students for many years. In addition to having been Graduate Program Director, I serve on the Admissions committee of the program and have participated in the program's recruitment efforts. I am certainly very committed to ensuring that we maintain and enhance the training environment of the MCP/HBH and MSTP programs, we recruit every year a group of smart, dedicated and diverse students, and help them develop into successful scientists in different scientific careers in academia, industry, policy and teaching.

**B. Positions and Honors.****Professional Positions**

1986-1989 Predoctoral Fellowship from IKY (The Greek Foundation of Fellowships)  
 1989- 1992 Postdoc fellow, Microbiology and Immunology, UCSF (Advisor: Dr. P. Coffino)  
 1992 Lecturer, Dept of Biochemistry, University of Athens, Greece  
 1993-1997 Postdoc Res. Associate, Pharmacology, SUNY Stony Brook, N.Y. (Advisor: Dr. S. Strickland)  
 1993 NIH-NIDDKD Postdoctoral Award  
 1994-1995 IHFSPO Postdoctoral Award  
 1998- 2000 Res. Asst. Professor, Dept of Psychiatry, SUNY Stony Brook, NY  
 1998- Member of SUNY Stony Brook IACUC  
 1998-1999 Targeted Research Award, SUNY Stony Brook (Neurological Disease)  
 2002- 2004 Carol M. Baldwin Breast Cancer Research Award  
 2000- 2003 Assistant Professor, Dept of Pharmacological Sciences, SUNY Stony Brook, NY  
 2003- 2014 Director, Molecular and Cellular Pharmacology Graduate Program, SUNY Stony Brook, NY  
 2004- 2008 Associate Professor, Dept of Pharmacological Sciences, SUNY Stony Brook, NY  
 2004 - 2010 Scientific advisory board of National Parkinson Foundation  
 2006- 2010 Established Investigator Award of the American Heart Association (National)  
 2007- 2010 Dean's Leadership Advisory Group

Program Director/Principal Investigator (Last, First, Middle):

- 2007 Dean's award for excellence in service to Graduate Education by a graduate program director  
 2008 - Professor, Dept of Pharmacological Sciences, SUNY Stony Brook, NY  
 2011 - Chair, Stony Brook University IACUC  
 2011 - President, Stony Brook University Hellenic Studies Center  
 2012 - Director of Stony Brook University Scholars in BioMedical Sciences (Med-into-Grad) Program

**Study Sections:** Grant Reviewer for Alzheimer's Association (2002-present); AHA-EIA (2011); NIH/NSC-C (2004); NIH/NST2 (2005-2009); NIH/SRB-M (2006); NIH/BDCN-90L/BINP (2004-2010, 2011); ZHD1 DRG-D (2011); AHA-Brain 1 (2007-); NIH-TWDA (2014-); NSF-GRFP (2014-)

1. S.E. Tsirka, A. Gualandris, D.G. Amaral, S. Strickland (1995) Excitotoxin-induced neuronal degeneration and seizure are mediated by tissue-type plasminogen activator. *Nature* 377:340-344.
2. Y.-P. Wu, C.-J. Siao, W. Lu, T.-C. Sung, M.A. Frohman, P. Milev, T.H. Bugge, J.L. Degen, J.M. Levine, R.U. Margolis, S.E. Tsirka. (2000) The tPA/plasmin extracellular proteolytic system regulates hippocampal mossy fiber reorganization through a novel proteoglycan substrate. *J. Cell Biol.* 148:1295-1304
3. M.M. Siddiq, and S.E. Tsirka. (2004) Tissue plasminogen activator and zinc are reciprocal antagonists of neurotoxicity. *Mol. Cell. Neurosci.* 25:162-171.
4. Emmetsberger J, Mirrione MM, Zhou C, Siddiq M, Fernandez-Monreal M, Ji K, SE Tsirka (2010) Tissue Plasminogen Activator alters intracellular sequestration of zinc through interaction with the transporter ZIP4, *J. Neurosci.* 30(19):6538-47 PMID: PMC2872103
5. Ji K, Akgul G, Wollmuth LP, Tsirka SE. (2013) Microglia actively regulate the number of functional synapses. *PLoS One*.8(2):e56293.
6. Nissen JC, Selwood D, Tsirka SE (2013) Tuftsin signals through its receptor neuropilin-1 via the transforming growth factor beta pathway. *J Neurochem*, 127(3):394-402.
7. Abraham AB, Bronstein R, Reddy AS, Maletic-Savatic M, Aguirre A, Tsirka SE. (2013) Aberrant Neural Stem Cell Proliferation and Increased Adult Neurogenesis in Mice Lacking Chromatin Protein HMGB2. *PLoS One*. 8(12):e84838.
8. Yao Y, Tsirka SE. (2011) Mouse MCP1 C-terminus inhibits human MCP1-induced chemotaxis and BBB compromise. *J Neurochem*. 118(2):215-23. PMID: PMC3129361

#### **Additional publications relevant to the field**

9. S.E. Tsirka, A.D. Rogove, S. Strickland (1996) Tissue plasminogen activator and neuronal cell death. *Nature* 384:123-124.
10. A.D. Rogove, S.E. Tsirka. (1998) Neurotoxic responses by microglia elicited by excitotoxic injury in the mouse hippocampus. *Curr.Biol.*8: 19-25.
11. Yao Y and Tsirka SE. Removal of the C-terminal domain of MCP1 by plasmin allows for the formation of a potent chemokine gradient (2010) *J. Biol. Chem*, 285(41):31509-16. PMID: PMC2951225
12. Sierra A, Encinas JM, Deudero JJP, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Tsirka SE, Maletic-Savatic M (2010) Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell*, 7:483-95 NIHMS233563
13. Talos F, Abraham A, Vaseva A, Holembowski L, Tsirka SE, Scheel A, Bode D, Dobbelsstein M, Bruck W, Moll UM (2010) p73 is an Essential Regulator of Neural Stem Cell Maintenance in Embryonal and Adult CNS Neurogenesis. *Cell Death Diff*, 17:1816-29 NIHMS263398
14. Bukhari N, Torres L and Tsirka SE. (2011) Axonal Repair in Spinal Cord Injury via Chondroitinase and the Tissue Plasminogen Activator (tPA)/Plasmin System, *J. Neurosci*, 31(42):14931-43. NIHMS333768.
15. Vaseva, AV, Holzmann, S, Ji, K, Tsirka, SE and Moll, UM (2012) p53 protein regulates the mitochondrial permeability transition pore during oxidative stress-induced necrosis and ischemic stroke. *Cell*, 149(7):1536-48

#### **D. Research Support**

Active

Program Director/Principal Investigator (Last, First, Middle):

2014-19 NASA: Remote, In Situ and Synchrotron Studies for Science and Exploration (RIS<sup>4</sup>E) PI: Glotch, (Role: Co-I, \$25K/year)

2014-2017 NIH-IRACDA: postdoctoral fellowship for Jillian Nissen (\$45K/year)

2013-2015: SUNYRF Reach: Pilot grant, effects of minocycline and NAC on microglia. PIs: Bergold, Feltri, Tsirka (\$25K)

2014-2016 "Evaluation of the effectiveness of a specially formulated hydrogel to prevent tissue adhesions after surgical intervention". PI: Tsirka (\$40K/year, Targeted Research Opportunities, SBU)

2014-2017 Institutionally-awarded research funds. PI: Tsirka (\$98K/year, SBU)

#### Completed

2012-2014 AHA predoctoral fellowship for Robert Bronstein

2012-2014 Turner predoctoral dissertation fellowship for Luisa Torres

2013-2014: SUNYRF Reach: Pilot collaborative grant assessing the effects of minocycline and NAC on microglia. PIs: Bergold, Feltri, Tsirka

2007-2013 NIH R01NS42168 Microglial effector pathways, PI: Tsirka

2012-2013 NMSS Modulation of T Cell Responses by Microglia During Experiments Allergic Encephalomyelitis (EAE) PI: Tsirka

2007-2012 NMSS, Center Grant from National Multiple Sclerosis Society, (with CoPIs Drs Levine, Colognato, Maletic-Savatic, and van Nostrand)

#### Pending

NIH R01: Role of Phospholipase D3 in late-onset Alzheimer's Disease. PIs: Frohman, Tsirka, van Nostrand

NIH R21: Modulation of neuronal activity by microglia. PIs: Tsirka, Wollmuth

NIH R01: Neurogenesis after stroke - the role of microglia. PI: Tsirka

#### Non Research / Graduate Training

NIH T32 GM0075186 Training Grant in Pharmacological Sciences (Principal Investigator: Styliani-Anna E. Tsirka)

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Powers, Robert Scott

eRA COMMONS USER NAME (credential, e.g., agency login): powerss

POSITION TITLE: Professor of Pathology and Director of Clinical Cancer Genomics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Carleton College, Minnesota	B.A.	05/1974	Mathematics
Columbia University, New York	Ph.D.	03/1983	Biological Sciences
Cold Spring Harbor Laboratory, New York	Postdoctoral	12/1985	Molecular Biology

**A. Personal Statement**

My role in this proposal will be to serve as a research mentor for the Scholars in BioMedical Sciences in Cancer Health Disparities. As a close colleague of Drs. McCombie and Tuveson at Cold Spring Harbor Laboratory, I believe that I can facilitate future development of translational projects involving both SUNY and CSHL for graduate students seeking further training in translational research.

I have been performing cancer genomics research since 1995. My main focus has been to use genome-wide DNA copy number profiling to identify recurrent amplified driver genes and to perform in vitro and in vivo analysis to validate their functional role in oncogenesis. My discoveries in this area include gene amplification of *PPM1D* and *ACK1* in breast and prostate adenocarcinomas and more recently activation of *FGF19* and *POFUT1* by genomic amplification and overexpression in hepatocellular carcinoma. I have experience in building collaborative research teams and am the PI of a multiple investigator NCI-funded Cancer Target Discovery and Validation Center (<http://ocg.cancer.gov/programs/ctd2>). This center continues to develop and apply methods to discover oncogenic drivers and dependencies based on analysis of human cancer genome data. In addition to copy number alterations in cancer, I have applied genome-wide methods to the study of mutational changes, epigenetic changes, and tumor-stromal interactions.

**B. Positions and Honors****Positions and Employment**

1974-1976 Computer Programmer, General Electric Co., NY  
 1977-1982 Graduate Research Assistant, Dept. of Biological Sciences, Columbia University  
 1982-1985 Postdoctoral Fellow, Cold Spring Harbor Laboratory, NY  
 1986-1988 Staff Investigator, Cold Spring Harbor Laboratory, NY  
 1988-1992 Assistant/Associate Professor, Dept. of Biochemistry, Robert Wood Johnson Medical School  
 1992-1995 Senior Scientist, Onyx Pharmaceuticals, CA  
 1995-2004 Scientific Director, Amplicon/Tularik Genomics Division, NY  
 1995-2004 Adjunct Associate Professor, Cold Spring Harbor Laboratory, NY  
 2004- 2014 Director, Human Cancer Genome Center & Associate Professor, CSHL  
 May 1 2014 Research Professor, Cold Spring Harbor Laboratory  
 May 1 2014 Professor, Department of Pathology, Stony Brook University, NY  
 May 1 2014 Director, Cancer Genomics, Cancer Center, Stony Brook University, NY

## **Honors and Professional Memberships**

1982-1985	Postdoctoral Fellowship Award, Leukemia Society of America
1988-1992	Editorial Board, Molecular and Cellular Biology
1989	Basil O'Conner Award
1992	A.C.S. Study Section (Molecular Biology)
2007	NCI Molecular Biology Program Project Study Section
2006-2013	NCI Cancer Genetics Study Section
2010-	Scientific Advisory Board, Hope Funds for Cancer Research
2014-	Chair, NCI Cancer Genetics Study Section

## **C. Contributions to Science**

1. **Identification and characterization of evolutionarily conserved genes in the RAS pathway.** I initiated the yeast *RAS* project as a postdoctoral fellow at Cold Spring Harbor in 1983, and continued these studies as an independent investigator through 1995. Although the downstream biochemical effector of RAS proteins was not conserved (adenyl cyclase in yeast, RAF and others in mammalian cells), the upstream activator CDC25 and the enzymes responsible for protein prenylation were highly conserved. Their discovery and study in yeast contributed to understanding their function in all eukaryotes.
  - a. Powers S, Kataoka T, Fasano O, Goldfarb M, Strathern J, Broach J, Wigler M. (1984) Genes in *S. cerevisiae* encoding proteins with domains homologous to the mammalian ras proteins. *Cell*.**36**:607-12.
  - b. Powers S, Michaelis S, Broek D, Santa Anna S, Field J, Herskowitz I, Wigler M. (1986) RAM, a gene of yeast required for a functional modification of RAS proteins and for production of mating pheromone  $\alpha$ -factor. *Cell*.**47**:413-22.
  - c. He B, Chen P, Chen SY, Vancura KL, Michaelis S, Powers S. (1991) RAM2, an essential gene of yeast, and RAM1 encode the two polypeptide components of the farnesyltransferase that prenylates  $\alpha$ -factor and Ras proteins. *Proc Natl Acad Sci U S A*.**88**:11373-7.
  - d. Lai CC, Boguski M, Broek D, Powers S. (1993) Influence of guanine nucleotides on complex formation between Ras and CDC25 proteins. *Mol Cell Biol*.**13**:1345-52.
2. **Developed and implemented methods that integrate genomic and functional analysis to identify and validate amplified driver genes in cancer.** In the early 2000s, my lab pioneered the oncogene discovery approach of using genome-wide DNA copy number profiling technologies (e.g. RDA, array CGH) together with mapping amplicon epicenters, expression analysis, and functional tests both in vitro and in vivo for oncogenic activity. Unlike other target discoveries in preclinical cancer research, all of our amplified oncogene discoveries have been independently validated.
  - a. Li J, Yang Y, Peng Y, Austin RJ, van Eyndhoven WG, Nguyen KC, Gabriele T, McCurrach ME, Marks JR, Hoey T, Lowe SW, Powers S. (2002) Oncogenic properties of PPM1D located within a breast cancer amplification epicenter at 17q23. *Nat Genet*.**31**:133-4.
  - b. Pei L, Peng Y, Yang Y, Ling XB, Van Eyndhoven WG, Nguyen KC, Rubin M, Hoey T, Powers S, Li J. (2002) PRC17, a novel oncogene encoding a Rab GTPase-activating protein, is amplified in prostate cancer. *Cancer Res*.**62**:5420-4.
  - c. Mu D, Chen L, Zhang X, See LH, Koch CM, Yen C, Tong JJ, Spiegel L, Nguyen KCQ, Servoss A, Peng Y, Pei L, Marks JR, Lowe SW, Hoey T, Jan LY, McCombie WR, Wigler MH, Powers S (2003) Genomic amplification and oncogenic properties of the KCNK9 potassium channel gene. *Cancer Cell*.**3**:297-302.
  - d. van der Horst EH, Degenhardt YY, Strelow A, Slavin A, Chinn L, Orf J, Rong M, Li S, See LH, Nguyen KQ, Hoey T, Wesche H, Powers S. (2005) Metastatic properties and genomic amplification of the tyrosine kinase gene ACK1. *Proc Natl Acad Sci U S A*.**102**:15901-6. PMID 1276100
3. **Focal copy number alterations contain multiple and interacting driver genes.** The paradigm for over 15 years has been that focal copy number alterations, particularly amplicons, have a single driver gene. Scott Lowe and I were the first to discover that focal amplicons can contain two driver genes (*YAP* and *BIRC2/IAP1*). Subsequently, my lab went on to show that one of the most common lung cancer amplicons at 14q13 contains three driver genes, *NKX2-1*, *NKX2-8*, and *PAX9*. Furthermore, we showed that these

three driver genes act synergistically in oncogenic assays. We also found that *FGF19*, only 50 kb distal to *CCND1*, is a co-driver gene of the 11q13 amplicon in liver cancer, and that these two genes functionally interacted in that *FGF19* controlled *CCND1* expression. It is now well established that most focal amplicons contain multiple driver genes, but the importance of functional interaction of multiple driver genes is still largely unappreciated.

- a. Zender L, Spector MS, Xue W, Flemming P, Cordon-Cardo C, Silke J, Fan ST, Luk JM, Wigler M, Hannon GJ, Mu D, Lucito R, Powers S, Lowe SW. (2006) Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. *Cell*.**125**:1253-67. PMID 3026384
- b. Kendall J, Liu Q, Bakleh A, Krasnitz A, Nguyen KC, Lakshmi B, Gerald WL, Powers S, Mu D. (2007) Oncogenic cooperation and coamplification of developmental transcription factor genes in lung cancer. *Proc Natl Acad Sci U S A*.**104**:16663-8. PMID 2034240
- c. Sawey ET, Chanrion M, Cai C, Wu G, Zhang J, Zender L, Zhao A, Busuttil RW, Yee H, Stein L, French DM, Finn RS, Lowe SW, Powers S. (2011) Identification of a therapeutic strategy targeting amplified *FGF19* in liver cancer by Oncogenomic screening. *Cancer Cell*.**19**:347-58. PMID 3061399

**4. Discovery of a targeted therapeutic strategy for *FGF19*-amplified hepatocellular carcinomas.** My lab discovered that amplification and overexpression in hepatocellular carcinomas of *FGF19*, encoding a secreted peptide that is a hepatocyte-specific mitogen, confers a strong selective Fgf19 signaling dependency. This suggested a targeted therapeutic strategy where hepatocellular carcinomas harboring *FGF19* amplification (approximately 15%) be treated with antibody inhibitors of Fgf19. Although the original anti-Fgf19 monoclonal antibody developed by Genentech that we studied was subsequently found to have unacceptable toxicity, two pharmaceutical companies have since then developed inhibitors of Fgf19's receptor (Fgfr4) that are less toxic and one, based on our study and validation by independent laboratories, is proceeding with clinical trials in HCC using *FGF19* amplification as a selective biomarker.

- a. Sawey ET, Chanrion M, Cai C, Wu G, Zhang J, Zender L, Zhao A, Busuttil RW, Yee H, Stein L, French DM, Finn RS, Lowe SW, Powers S. (2011) Identification of a therapeutic strategy targeting amplified *FGF19* in liver cancer by Oncogenomic screening. *Cancer Cell*.**19**:347-58. PMID 3061399

#### Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40132415/?sort=date&direction=ascending>

#### D. Research Support

##### Ongoing Research Support

U01CA168409 NIH (Powers) Role: PI 05/1/12-04/30/17

Computational and functional approaches to validating cancer genome targets.

Goal: Computationally analyze cancer genome data to guide functional screening of candidate oncogenic drivers and dependencies in model systems.

##### Completed Research Support

U01CA168409 NIH (Sander) Role: Co-investigator 05/01/12-04/30/14

Supplement for Computational and Functional Approaches to Validating Cancer Genome Targets.

Goal: Develop Dashboard (Web Interface) to Display CTD2 Data

R01CA124648 NIH (Powers) Role: PI 12/1/06-11/30/12

An integrative approach to cancer gene discovery in hepatocellular carcinoma

Goal: Use comparative genomics of human and mouse liver cancer to discover driver genes.

P01 CA013106 NIH (Hannon) Role: Core Director 02/10/05-12/31/13

CSHL Tumor Virus Grant YR 41 Genome & Proteomics Core D

Goal: Directing the Genome & Proteomics facility of the DNA Tumor Virus grant.

RC2CA148532-02 NIH (Powers) Role: PI 09/29/09-08/31/12

### CSHL Molecular Target Discovery and Development Center

This center uses informatic analysis of TCGA data coupled to functional tests in transplantable mouse models to discover new driver genes that underlie the diversity of genomic alterations found in human cancer.

U01CA105388      NIH (Lowe)      Role: Co-investigator      09/1/09-08/31/14

Identifying driver mutations and tumor dependencies by comparative oncogenomics.

Goal: Use oncogenomic screening in mouse models to discover oncogenes and tumor suppressor genes that drive human cancer development and to use synthetic lethal RNAi screens to discover tumor dependencies.

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Lina M. Obeid</b>	POSITION TITLE <b>Professor</b>		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>obeidl</b>			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Rutgers University, Piscataway, NJ	B.S.	1978	Chemistry
American University Beirut, Lebanon	M.D	1983	Medicine
Duke University, Durham, NC	Residency	1983-1987	Internal Medicine
Duke University, Durham, NC	Fellow	1988-1990	Endocrinology

**NOTE: The Biographical Sketch may not exceed four pages.**

### A. Personal Statement

I have the expertise, leadership and motivation necessary to successfully carry out my role as a mentor on this grant application. I have a broad background in Medicine, biochemistry, cell and molecular biology with specific training and expertise in bioactive sphingolipid metabolism and role in cell regulation. In my medical training I gained significant expertise in pathophysiology of disease. As a postdoctoral fellow, I carried out biochemical and molecular and cellular biology studies on G-protein coupled receptors and protein kinase C. As an Assistant and Associate professor at Duke University, I established my research program to investigate the metabolism and role of bioactive lipid mediators in cell regulation, apoptosis and senescence. For the last decade as a Professor in Medicine, Biochemistry and Molecular Biology, I have consolidated my research program and expanded my studies into the role and regulation of bioactive lipids in disease pathobiology with a focus on inflammation, cancer and aging. As PI on several previous VA and NIH-funded grants, I successfully administered the projects and collaborated with other researchers. As a result of these previous experiences, I am aware of the importance of collaboration and communication in science, and of the value of shared instrumentation.

Moreover, through out my career I have been involved in the clinical training of medical students and residents, as well as, the research training of numerous students (in my laboratory and served on thesis advisory committee), post doctoral fellows, and junior faculty. Most of my trainees are in academic positions ranging from assistant and associate professors, staff scientists, and research fellows. I also have significant experience in teaching both in a didactic and in a non-classroom environment. In addition for over 5 years I was Associate Director of the NIH-funded MUSC Medical Scientist Training Program (MSTP), and for the last 10 years I served as PI on a Center of Biomedical Research Excellence (COBRE) in Lipidomics and Pathobiology. All of this extensive experience in training at multiple academic levels has prepared me to have a leadership role as a mentor on this proposal.

In summary, I have a demonstrated record of successful and productive research projects in an area of high relevance for disease, and my expertise and experience have prepared me to lead research projects and to be a mentor for more junior scientists at all levels.

### B. Positions and Honors

1990 - 1992	Associate, Department of Medicine, Duke University
1990 - 1998	Staff Physician Durham Veterans Affairs Medical Center
1992 - 1996	Assistant Professor, Department of Medicine, Duke University
1994 - 1998	Assistant Professor, Department of Cell Biology, Duke University
1996 - 1998	Associate Professor: Department of Medicine, Duke University
1998 - 2012	Staff Physician Ralph H Johnson Veterans affairs Medical Center
1998 - 2012	Boyle Professor of Medicine, Department of Medicine, Medical University of South Carolina

1998 - 2012 Professor, Department of Biochemistry, Medical University of South Carolina  
 2002 - 2011 Associate Director for Aging Biology, Center of Aging, Medical University of South Carolina  
 2002 - 2011 Associate Director, Medical Scientist Training Program, Medical University of South Carolina  
 2012 - Professor of Medicine, Stony Brook University  
 2012 - Dean for Research, Stony Brook University  
 2012- Staff Physician Northport Veterans Affairs Medical Center

**Honors and Awards:** B.S. with honors 1978; Dean's honor list, School of Medicine 1978-83; Member, Alpha Omega Alpha, Honor Medical Society 1982; M.D. with distinction from American University of Beirut, School of Medicine 1983; Hartford Scholar 1989-90; Henry Christian Memorial Award 1990; Clinical Investigator Award, National Institute of Aging 1992-97; James A. Shannon Director's Award 1994-96; Paul Beeson Physician Faculty Scholar 1995-98; First Award, National Institute of Aging 1995-00; Veterans Affairs Merit Award 2000-present; 2002 Elected to membership of Association of American Physicians; AAAS Fellow (2004). JLR lectureship awardee for the FASEB lysophospholipid meeting, august 2013.

**Study Sections:** Veteran's Administration (Ad hoc reviewer); National Science Foundation Ad hoc reviewer; American Federation of Aging Research (Beeson Program, Scientific Advisory Board, 1999 - 2005); American Federation of Aging Research (AFAR) Research Committee Review board (2003-present); AFAR (Atlanta Affiliate, 2003 - present); National Cancer Institute (NCI)-Special Panel for PPG, 1999 & 2001; National Cancer Institute (NCI) Special Panel for RFA CA00-002, 2000; NIH: Permanent Member of Medical Biochemistry then Physiological Chemistry study sections, 2001 – 2005. NIH:Special Emphasis Panel/Scientific Review Group ZRG1 BCMB-S (02) M 2011. NCI Special Emphasis Panel – Provocative Question B, 2013. RFA RM-11016: Regional Comprehensive Metabolomics Resource Cores ZRG1 BST-F (50) R, 2013.

### C. Selected Peer-reviewed Publications (pubs selected from recent pubs and out of ~200 total)

1. Johnson, K.R., Johnson, K.Y., Crellin, H.G., Ogretmen, B., Boylan, A.M., Harley, R.A., and **Obeid, L.M.** (2005) Immunohistochemical Distribution of Sphingosine Kinase 1 in Normal and Tumor Lung Tissue. *JHC* 53(9): 1159-1166.
2. Taha, T.A., Kitatani, K., El-Alwani, M., Bielawski, J., Hannun, Y.A., and **Obeid, L.M.** (2006) Loss of sphingosine kinase-1 activates the intrinsic pathway of programmed cell death: modulation of sphingolipid levels and the induction of apoptosis. *FASEB* 20(3):482-4.
3. Spassieva, S., Bielawski, J., Anelli, V., and **Obeid, L.M.** (2007) Chapter 12: Combination of C17 Sphingoid Base Homologues and Mass Spectrometry Analysis as a New Approach to Study Sphingolipid Metabolism. In *Methods Enzymology*. Volume 434 Lipidomics and Bioactive Lipids: Lipids and Cell Signaling, Brown, H.A (Ed.) ISBN: 978-0-12-373965-0.
4. Anelli, V., Gault, C.R., Cheng, A.B., and **Obeid, L.M.** (2008) Sphingosine Kinase 1 is Up-regulated During Hypoxia in U87MG Glioma Cells: Role of Hypoxia-inducible Factors 1 and 2. *J Biol Chem.* FEB 8; 283(6): 3365-75. **\*PMCID Not applicable to this publication.**
5. Hannun, Y.A., and **Obeid, L.M.** (2008) Principles of bioactive lipid signaling: lessons from sphingolipids. *Nature Reviews Molecular Cell Biology*. Feb 9; (2):139-50. **\*PMCID Not applicable to this publication.**
6. Hammad, S., Crellin, H., Wu, X., Melton, J., Anelli, V., and **Obeid, L.M.** (2008) Dual and Distinct Roles for Sphingosine Kinase 1 and Sphingosine 1 Phosphate in the Response to Inflammatory Stimuli in RAW Macrophages. *POLM*. Mar; 85(3-4):107-14. **PMCID: PMC2290737**
7. Novgorodov, S.A., Gudiz, T.I., **Obeid, L.M.** (2008). Long-Chain Ceramide Is A Potent Inhibitor of the Mitochondrial Permeability Transition Pore. *J Biol Chem.*, Sep 5; 283(36):24707-17. **PMCID: PMC2529003**

8. Snider, A.J., Kawamori, T., Bradshaw, S.G., Orr, K.A., Gilkeson, G., Hannun, Y.A., and **Obeid, L.M.** (2009) A Role For Sphingosine Kinase 1 in Dextran Sulfate Sodium-Induced Colitis. *FASEB* Jan; 23(1):143-52. **PMCID: PMC2626622**

9. Kawamori, T., Kaneshiro, T., Okumura, M., Maalouf, S., Uflacker, A., Bielawski, J., Hannun Y.A., **Obeid L.M.** (2009) Role for sphingosine kinase 1 in colon carcinogenesis. *FASEB* Feb; 23(2):405-14. **PMCID: PMC2630788**

10. Spassieva, S.D., Mullen, T.D., Townsend, D.M., and **Obeid, L.M.** (2009) Disruption of ceramide synthesis by CerS2 down-regulation leads to autophagy and the unfolded protein response. *Biochem. J.* 2009 Sep 3. **PMCID: PMC19728861**

11. Siskind LJ, Mullen TD, Rosales KR, Clarke CJ, Hernandez-Corbacho MJ, Edinger AL, **Obeid LM.** The BCL-2 protein BAK is required for long-chain ceramide generation during apoptosis. *J Biol Chem.* 2010 Feb 18. [Epub ahead of print] PMID: 20172858. **PMCID: PMC2825918.**

12. Heffernan-Stroud LA, **Obeid LM.** p53 and regulation of bioactive sphingolipids. *Adv Enzyme Regul.* 2011;51(1):219-28. **PMCID:PMC3078951**

13. Heffernan-Stroud, L. A., Helke, K.L., Jenkins, R.W., DeCosta, A.M., Hannun, Y.A., and **Obeid, L.M.** (2011) Defining a role for sphingosine kinase 1 in p53-dependent tumors. *Oncogene.* 2012 Mar 1;31(9):1166-75. doi: 10.1038/onc.2011.302. Epub 2011 Jul 18. **PMCID:PMC3278571**

14. Chipuk JE, McStay GP, Bharti A, Kuwana T, Clarke CJ, Siskind LJ, Obeid LM, Green DR. (2012) Sphingolipid metabolism cooperates with BAK and BAX to promote the mitochondrial pathway of apoptosis. *Cell.* 2012 Mar 2;148(5):988-1000. **PMID: 22385963**

15. Snider AJ, Wu BX, Jenkins RW, Sticca JA, Kawamori T, Hannun YA, **Obeid LM.** Loss of neutral ceramidase increases inflammation in a mouse model of inflammatory bowel disease. *Prostaglandins Other Lipid Mediat.* 2012 Dec;99(3-4):124-30. doi: 10.1016/j. prostaglandins 2012.08.003. Epub 2012 Aug 31.

16. Gault CR, Eblen ST, Neumann CA, Hannun YA, **Obeid LM .** Oncogenic K-Ras regulates bioactive sphingolipids in a sphingosine kinase 1-dependent manner. *J Biol Chem.* 2012 Sep 14;287(38):31794-803. **PMCID: PMC3442513**

17. Gandy KA, Canals D, Adada M, Wada M, Roddy P, Snider AJ, Hannun YA, **Obeid LM.** Sphingosine 1-phosphate induces filopodia formation through S1PR2 activation of ERM proteins. *Biochem J.* 2013 Feb 1;449(3):661-72. doi: 10.1042/BJ20120213. PMID: 23106337

18. Orr Gandy KA, Adada M, Canals D, Carroll B, Roddy P, Hannun YA, **Obeid LM.** Epidermal growth factor-induced cellular invasion requires sphingosine-1-phosphate/sphingosine-1-phosphate 2 receptor-mediated ezrin activation. *FASEB J.* 2013 Apr 29.

## D. Research Support

### Ongoing

1) Merit Award (Obeid - PI) 10/1/10 - 09/30/2017

Agency: Veteran's Administration

"Bioactive Sphingolipid enzymes as targets in inflammation"

The long-term goal of this project is to define the role of ceramidases and sphingosine kinase in inflammation and to target these enzymes for novel anti-inflammatory therapy.

2) 9R01GM097741-13A1 (Obeid - PI) 3/1/12-5/31/15

Agency: NIGMS (The competing renewal of this grant scored in the 13th% and is expected to be funded)  
Role and Regulation of Ceramide Synthases in Apoptosis

The aims of this proposal is to dissect the role of the novel family of Ceramide Synthases in regulation of specific and distinct pools of ceramide and their role in apoptosis. Moreover this proposal will dissect the role of Bak in regulation of ceramide metabolism.

3) P01 CA097132-11 (Hannun – PI, Obeid - Project 3 Leader)  
09/01/014-08/31/19

Agency: NIH/NCI  
Sphingolipids in Cancer Biology and Therapy

The aims of this proposal are to study the role of sphingosine kinase in p53 null and mutant cancer development.

## Completed

1) P20 RR17677 (Obeid - PI) 09/26/02 - 04/1/12

Agency: NIH/NCRR

"COBRE in Lipidomics and Pathobiology"

To develop an interactive Center of Lipidomics and Pathobiology that will promote the growth and excellence of research at MUSC. This involves mentoring 5 junior investigators in their respective projects in the area of lipidomics and pathology, as well as three cores.

2) P30 CA138313-01 (Kraft - PI) 04/1/09-03/31/14

Agency: NIH/NCI

Medical University of South Carolina-Cancer Center Support Grant

Leader of Program Lipid signaling in cancer

Major goal: To support the ongoing research infrastructure, research programs, shared resources, developmental funds, and administration of the Hollings Cancer Center at the Medical University of South Carolina to ensure the development of more effective approaches to cancer prevention, diagnosis, and therapy.

3) IR01-GM-62887 (Obeid - PI) 5/01/01 – 8/31/11

Agency: NIH/NIA

"Sphingosine Phosphate in Inflammation"

The main goals of this proposal were focused on the role of sphingosine kinase 1 and sphingosine phosphate in inflammation.

4) 1R01-AG-16583 (Obeid - PI) 09/01/01-08/31/11

Agency: NIH/NIA

"Mitochondrial Ceramide in Chemotherapy-induced Apoptosis"

The long-term goal of this proposal is to develop ceramides as novel therapeutic approaches to cancer treatment. The sphingolipid ceramide has recently emerged as a key regulator of apoptosis in response to multiple inducers such as chemotherapeutic agents, UV radiation, and tumor necrosis factor alpha.

5) Merit Award (Obeid - PI) 01/1/04 - 12/31/08

Agency: Veteran's Administration

"Regulation of Human Alkaline Ceramidases and Role in Cancer Biology "

Specific aims of this grant are to clone two other human homologues of alkaline phytoCDase and determine their enzymatic function in cells and *in vitro*. To study the biochemical and cellular regulation of the two new putative alkaline CDases. To determine the differential regulation and role of the different alkaline CDases in regulation of apoptosis.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Hussain, M. Mahmood

POSITION TITLE: Professor

eRA COMMONS USER NAME (credential, e.g., agency login): mhussain

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Osmania University, Hyderabad, India	M. Sc.	1978	Biochemistry
University of Hyderabad, India	M. Phil.	1979	Intestinal absorption
Oklahoma State University, USA	Ph.D.	1984	Biochemistry
University of Copenhagen, Denmark	Lic. Med.	1986	Biochemistry

**A. Personal Statement**

I joined the Medical College of Pennsylvania as an Assistant Professor in 1991. Since then, my laboratory has been studying lipid absorption and lipoprotein assembly. My laboratory has developed several methods and models to study chylomicron assembly and secretion. We studied secretion of lipids with chylomicrons and showed that newly synthesized triglycerides are preferentially secreted with chylomicrons. We described mechanisms for the absorption and transport of vitamins A and E. We have shown that there are two pathways (apoB-dependent and -independent) involved in cholesterol absorption. Further, we have documented the importance of MTP, ABCA1, ACAT2, apoA1, and apoAIV in these pathways.

Since MTP is an essential chaperone for the assembly of chylomicrons, we have paid much attention to its role in lipoprotein assembly. We studied protein-protein interactions between apoB and MTP, demonstrated two independent functional domains that carry out lipid transfer and apoB binding activities in MTP, and discovered that binding of MTP to lipid vesicles enhances its binding with apoB. We showed that MTP was evolved as a phospholipid transfer protein and acquired triglyceride transfer activity during a transition from invertebrates to vertebrates. Also, provided molecular and biochemical explanations for some missense mutations found in abetalipoproteinemia subjects. We have developed new assays to measure MTP activity using fluorescent lipids. In addition, we showed that MTP transfers phospholipids onto CD1d. In short, I have a long history and demonstrated expertise to study MTP, lipid absorption, and lipoprotein assembly and secretion.

Recently, we revealed that lipid absorption is regulated by circadian rhythms and disruptions in these rhythms causes hyperlipidemia and enhances atherosclerosis in mice. We have also identified a novel regulator, Ire1<sup>2</sup>, of intestinal lipid absorption. We showed that Ire1<sup>2</sup> regulates MTP expression in the intestine involving post-transcriptional degradation of mRNA. Moreover, we have identified that microRNA-30c regulates lipoprotein production without causing steatosis. We showed overexpression of miR-30c in the livers of mice reduces plasma lipids and atherosclerosis suggesting that it might be a better agent than MTP inhibitors to reduce plasma lipids.

Over the years, I have published 106 peer-reviewed papers and 38 reviews. I have served as the principal investigator on several NIH and AHA grants over the past 25 years. I have managed research groups consisting of visiting scientists (10), clinical fellows (9), junior faculty (3), postdoctoral fellows (17), graduate students (14, including 6 MD, PhD students), rotating students (21), under graduate students (18), and technicians (7), and have ample experience in hiring, training, safety, budget etc. Moreover, I have

collaborated with several national and international researchers and produced several peer-reviewed publications. Hence, I have demonstrated track-record and experience to lead the proposed project.

### **Positions:**

6/87-9/91 Staff Research Investigator, Gladstone Institute for Cardiovascular Disease, UCSF, CA  
 10/91-6/95 Assistant Professor, Pathology and Biochemistry, the Medical College of Pennsylvania  
 7/95-9/99 Associate Professor, MCP Hahnemann University, Philadelphia, PA  
 10/99-4/02 Associate Professor, SUNY Downstate Medical Center, Brooklyn, NY  
 4/02-present Professor, SUNY Downstate Medical Center, Brooklyn, NY  
 4/03-present President, Chylos, Inc., Woodbury, NY  
 09/13-present Research Scientist, VA New York Harbor Healthcare System, Brooklyn, NY  
 05/14-present Distinguished Professor, State University of New York, NY

**Other Experience and Professional Memberships:** Premium professional silver heart member, AHA, Dallas, TX (2005); Editorial board member, Journal of Lipid Research (2008-present); Co-Editor-in-Chief, Nutrition & Metabolism (London) (2004-2008), Editor-in-Chief, Nutrition & Metabolism (London) 2009-present; Editorial board member, Atherosclerosis, thrombosis, and vascular biology (2009-present);

**Grant review committees:** American Heart Association, Southeastern PA Affiliate (1995-1997); Northeast Consortia Peer Review Study Group 2, AHA (2000-2005); Ad hoc reviewer for the NIH: from 1999 to present; WHO Regional Office for Europe, Copenhagen, Denmark (2000); Member, Endocrinology Merit Review Subcommittee, VA (2004-2010); Vice Chair, NE2 Study Group, AHA (2004); Chairman, Northeast 2 Study Group, AHA (2005); AHA National Center (2007-2009); Medical research council, UK (2011); French national research agency (2012-present); Chair, NIH Study section ZDK1 GRB-N (2013);

**B. Honors:** National Merit Scholarship, Government of India (1976-1978); Danish International Development Fellow, Denmark (1980-1981); Boston University School of Medicine Research Award (1986); Irvine H. Page Award, Council on Arteriosclerosis, Thrombosis, and Vascular Biology, AHA (1998); Leonard N. Horowitz Research Award, AHA, Southeastern Pennsylvania Affiliate (1998); Established Investigator, AHA (1999-2002); Outstanding Achievement Award, International Journal of Oncology, Oncology Reports, International Journal of Molecular Medicine, Crete, Greece (2001); President, New York Lipid and Vascular Biology Research Club (2001-2002); Promising Inventor Award, The Research Foundation, SUNY, Albany, NY (2003); Chancellor's Research Recognition Award, The Research Foundation, State University of New York, Albany, NY (2003); Research administration volunteer research award, AHA, New Haven, CT (2005); Chancellor's award for excellence in scholarship and creative activities, Brooklyn, NY (2005); 2011 ATVB Special Recognition Award in Arteriosclerosis, American Heart Association, National Center

**C. Contribution to Science:** Different topics investigated and representative publications in each area are listed below.

### **Involvement of bone marrow in chylomicron remnant catabolism:**

1. **Hussain MM**, Mahley RW, Boyles JK, Fainaru M, Brecht WJ, and Lindquist P (1989) Chylomicron/chylomicron remnant clearance by liver and bone marrow in rabbits: Factors that modify tissue-specific uptake. **J Biol Chem** 264:9571-9582.
2. Mahley RW, Weisgraber KH, **Hussain MM**, Greenman B, Fisher M, Vogel T, and Gorecki M (1989) Intravenous infusion of apolipoprotein E accelerates clearance of plasma lipoproteins in rabbits. **J Clin Invest** 83:2125-2130.
3. Anderson LJ, Boyles JK, and **Hussain MM** (1989) A rapid method for staining large chylomicrons. **J Lipid Res** 30:1819-1824.
4. **Hussain MM**, Mahley RW, Boyles JK, Lindquist PA, Brecht WJ, and Innerarity TL (1989) Chylomicron metabolism: Chylomicron uptake by bone marrow in different animal species. **J Biol Chem** 264:17931-17938.

### **Role of receptors and proteoglycans in chylomicron remnant clearance:**

1. **Hussain MM**, Maxfield FR, Mas-Oliva J, Tabas I, Ji ZS, Innerarity TL, and Mahley RW (1991) Clearance of chylomicron remnants by low density lipoprotein receptor-related/ $\pm_2$ -macroglobulin receptor. **J Biol Chem**

266:13936-13940.

2. Ji ZS, Brecht WJ, Miranda RD, **Hussain MM**, Innerarity TL, and Mahley RW (1993) Role of heparan sulfate proteoglycans in the binding and uptake of apolipoprotein E-enriched remnant lipoproteins by cultured cells. **J Biol. Chem** 268:10160-10167.
3. **Hussain MM**, Innerarity TL, Brecht WJ and Mahley RW (1995) Chylomicron metabolism in normal, cholesterol-fed and Watanabe heritable hyperlipidemic rabbits: Saturation of the sequestration step of the remnant clearance pathway. **J Biol Chem.** 270:8578-8587.
4. **Hussain MM**, Glodberg IJ, Weisgraber KH, Mahley RW, and Innerarity TL (1997) Uptake of chylomicrons by the liver, but not by the bone marrow, is modulated by lipoprotein lipase activity. **Arterioscl Thromb Vasc Biol** 17:1407-1413.

#### **Assembly and secretion of lipids with chylomicrons:**

1. Luchoomun J, and **Hussain MM** (1999) Assembly and secretion of chylomicrons by differentiated Caco-2 cells: nascent triglycerides and preformed phospholipids are preferentially used for lipoprotein assembly. **J Biol Chem** 274:19565-19572.
2. **Hussain MM**, Kancha RK, Zhou Z, Luchoomun J, Zu H, Bakillah A (1996) Chylomicron assembly and catabolism: role of apolipoproteins and receptors. **Biochim Biophys Acta** 1300:151-170.
3. **Hussain MM** (2000) A proposed model for the assembly of chylomicrons. **Atherosclerosis** 148:1-15
4. **Hussain MM**, Kedees MH, Singh K, Athar H, Jamali NZ (2001) Signposts in the assembly of chylomicrons. **Front Biosci** 6:D320-D331.

#### **Secretion of fat-soluble vitamins with chylomicrons:**

1. Nayak N, Harrison EH, and **Hussain MM** (2001) Retinyl ester secretion by the intestinal cells is a highly specific and regulated process that is dependent on the assembly and secretion of chylomicrons. **J Lipid Res** 42: 272-280.
2. During A, **Hussain M M**, Morel DW, and Harrison EH (2002) Carotenoid uptake and secretion by Caco-2 cells: <sup>2</sup>-carotene isomer selectivity and carotenoids interactions. **J Lipid Res** 43:1086-1095.
3. Anwar K, Kayden HJ, and **Hussain MM** (2006) Transport of vitamin E by differentiated Caco-2 cells. **J Lipid Res** 47:1261-1273. Epub 2006 Mar 28.
4. Anwar K, Iqbal J, and **Hussain MM** (2007) Mechanisms involved in Vitamin E transport by primary enterocytes and in-vivo absorption. **J Lipid Res** 48:2028-2038. Epub 2007 June 20.

#### **ApoB-dependent and apoB-independent pathways of lipid absorption:**

1. Iqbal J, Anwar K and **Hussain MM** (2003) Multiple, independently regulated pathways of cholesterol transport across the intestinal epithelial cells. **J Biol Chem** 278:31610-31620. Epub 2003 May 29.
2. Iqbal J, and **Hussain MM** (2005) Evidence for multiple complementary pathways for efficient cholesterol absorption in mice. **J Lipid Res** 46:1491-1501. Epub 2005 April 16.
3. Iqbal J, Parks, JS, **Hussain MM** (2013) Lipid absorption defects in intestine-specific microsomal triglyceride transfer protein and ATP-binding cassette transporter A1 deficient mice. **J Biol Chem** 288:30432-30444. Epub 2013 Sept 09.
4. Iqbal J, Boutjdir M, Rudel LL, **Hussain MM** (2014) Intestine specific MTP deficiency with global ACAT2 gene ablation lowers acute cholesterol absorption with chylomicrons and high density lipoproteins. **J Lipid Res.** 55:2261-2275. Epub 2014 Jul 16.

#### **Methods to measure apolipoproteins and MTP activity:**

1. Bakillah A, Zhou Z, Luchoomun J, and **Hussain MM** (1997) Measurement of apolipoprotein B in various cell lines: correlation between intracellular levels and rates of secretion. **Lipids** 32:1113-1118.
2. Athar H, Iqbal J, Jiang XC, and **Hussain MM** (2004) A simple, rapid and sensitive fluorescence assay for microsomal triglyceride transfer protein. **J Lipid Res** 45:764-772. Epub 2004 Feb 1.
3. Rava P, Athar H, Johnson C, and **Hussain MM** (2005) Transfer of cholesteryl esters and phospholipids as well as net deposition by microsomal triglyceride transfer protein. **J Lipid Res** 46:1779-1785. Epub 2005 May 16.

#### **Protein-protein interactions between apoB and MTP:**

1. **Hussain MM**, Bakillah A, and Jamil H (1997) Apolipoprotein B binding to microsomal triglyceride transfer protein decreases with increases in length and lipidation: implications in lipoprotein biosynthesis.

### **Biochemistry 36:13060-13067.**

2. Bakillah A, Jamil H, and **Hussain M M (1998)** Lysine and arginine residues in the N-terminal 18% of apolipoprotein B are critical for its binding to microsomal triglyceride transfer protein. **Biochemistry** 37:3727-3734.
3. **Hussain MM**, Bakillah A, Nayak N, and Shelness GS (1998) Amino acids 430-570 in apolipoprotein B are critical for its binding to microsomal triglyceride transfer protein. **J Biol Chem** 273:25612-25615.
4. Bakillah A, and **Hussain MM (2001)** Binding of microsomal triglyceride transfer protein to lipids results in increased affinity for apolipoprotein B: Evidence for stable microsomal MTP/lipid complexes. **J Biol Chem** 276:31466-31473. Epub 2001 Jun 26.

### **Role of MTP's phospholipid transfer activity in lipoprotein assembly and secretion:**

1. Rava P, Ojakian GK, Shelness GS and **Hussain MM (2006)** Phospholipid transfer activity of microsomal triglyceride transfer protein is sufficient for the assembly and secretion of apolipoprotein B lipoproteins. **J Biol Chem** 281:11019-11027. Epub 2006 Feb. 13.
2. Rava P, and **Hussain MM (2007)** Acquisition of triacylglycerol transfer activity by microsomal triglyceride transfer protein during evolution. **Biochemistry**. 46:12263-12274. Epub 2007 Oct 09. PMID: 17924655.
3. Khatun I, Zeissig S, Iqbal J, Wang M, Curiel D, Shelness GS, Blumberg RS, **Hussain MM (2012)** Phospholipid transfer activity of microsomal triglyceride transfer protein produces apolipoprotein B and reduces hepatosteatosis while maintaining low plasma lipids in mice. **Hepatology**, 55:1356-1368. Epub 2012 Mar 20.

### **Contribution to the role of MTP in CD1D and NKT cells:**

1. Dougan SK, Salas A, Rava P, Agyemang A, Kaser A, Morrison G, Khurana A, Kronenberg M, Johnson C, Exley M, **Hussain MM**, Blumberg RS (2005) Microsomal triglyceride transfer protein: lipidation and control of CD1d on antigen presenting cells. **J Exp Med** 202:529-539. Epub 2005 Aug. 08.
2. Dougan SK, Rava P, **Hussain MM**, Blumberg RS (2007) MTP regulated by an alternate promoter is essential for NKT cell development. **J Exp Med** 204:533-545. Epub 2007 Feb 20.
3. Zeissig S, Murata K, Sweet L, Publicover J, Hu Z, Kaser A, Bosse E, Iqbal J, **Hussain MM**, Balschun K, Rocken C, Arlt A, Gunther R, Hampe J, Schreiber S, Baron JL, Moody DB, Liang TJ, Blumberg RS (2012) Hepatitis B virus-induced lipid alterations contribute to natural killer T cell-dependent protective immunity. **Nat Med** 18:1060-1068. Epub 2012 June 17.

### **Regulation of chylomicron assembly and intestinal lipid absorption by IRE1<sup>2</sup>:**

1. Iqbal J, Dai K, Seimon T, Jungreis R, Oyadomari M, Kuriakose G, Ron D, Tabas I, and **Hussain MM (2008)** IRE1<sup>2</sup> inhibits chylomicron production by selectively degrading MTP mRNA. **Cell Metabolism** 7:445-455. PMID: 18460335.
2. Dai K, Khatun I, and **Hussain MM (2010)** NR2F1 and Ire1<sup>2</sup> suppress MTP expression and lipoprotein assembly in undifferentiated intestinal epithelia cells. **Arterioscl Thromb Vasc Biol** 30:568-574. PMID: 20007910.
3. Iqbal J, Queiroz J, Li Y, Jiang XC, Ron D, **Hussain MM (2012)** Increased intestinal lipid absorption caused by Ire1<sup>2</sup> deficiency contributes to hyperlipidemia and atherosclerosis in Apolipoprotein E-deficient mice. **Circ Res** 110:1575-1584. Epub 2012 May 3.
4. **Hussain MM**, Leung TM, Zhou L, Abu-Merhi S (2013) Regulating intestinal function to reduce atherogenic lipoproteins. **Clinical Lipidology** 8:481-490.

### **Circadian regulation of plasma lipids:**

1. Pan X, and **Hussain MM (2007)** Diurnal regulation of microsomal triglyceride transfer protein and plasma lipid levels. **J Biol Chem** 282:24707-24719. Epub 2007 June 15.
2. Pan X, and **Hussain MM (2009)** Clock is important for food and circadian regulation of macronutrient absorption in mice. **J Lipid Res** 50: 1800-1813. Epub 2009 Apr 22. PMID: 19387090.
3. Pan X, Zhang Y, Wang L, and **Hussain MM (2010)** Diurnal regulation of MTP and plasma lipid by Clock is mediated by SHP. **Cell Metabolism**. 12:174-186. Epub 2010 Aug 4. PMID: 20674862
4. Pan X, Jiang XC, **Hussain MM (2013)** Impaired cholesterol metabolism and enhanced atherosclerosis in Clock mutant mice. **Circulation** 128:1758-1769. Epub 2013 Sept 06.

### **MicroRNAs regulating plasma lipids and lipoproteins:**

1. Soh J, Iqbal J, Queiroz J, Fernandez-Hernando C, **Hussain MM (2013)** MicroRNA-30c reduces hyperlipidemia and atherosclerosis in mice by decreasing lipid synthesis and lipoprotein secretion. **Nat. Med.** 19:892-900. Epub 2013 June 9.
2. Soh J, **Hussain MM (2103)** Supplementary site interactions are critical for the regulation of microsomal triglyceride transfer protein by microRNA-30c. **Nutr Metab (Lond).** 10:56. Epub 2013 Sept 04.
3. Irani S, **Hussain MM (2015)** Role of microRNA-30c in lipid metabolism, adipogenesis, cardiac remodeling and cancer. **Curr Opin Lipidol** In press.

## D. Research Support

### Ongoing Research Support

“Avoiding toxicity associated with MTP ablation” The aims are to find ways to avoid toxicities associated with MTP inhibition in mice as well as to recognize mechanisms involved in the toxicity associated with MTP inhibition in mice. NIH/NHLBI 3RO1 HL095924-03; 02-01-2010 to 01-31-2014. There is no overlap with the current application. This grant is in no-cost extension and will not be renewed. PI: M. Mahmood Hussain.

“Circadian regulation of lipid metabolism” The aims are to study the role of Bmal1 in the diurnal and food-entrained regulation of plasma lipids. Agency: NIH/NIDDK, RO1 DK081879-02; 07-01-2011 to 08-31-2015. There is no overlap with the current application. PI: M. Mahmood Hussain.

“Regulation of plasma lipids and atherosclerosis by miR-30c” The aims are to understand how miR-30c modulates hyperlipidemia and atherosclerosis and explain mechanisms involved in reducing plasma lipids by miR-30c. Agency: VA Merit Award BX1728; 04-01-2013 to 06-30-2017. There is no overlap with the current application. PI: M. Mahmood Hussain.

“Exploration of lipid transport proteins as drug targets for the treatment of tuberculosis” The goal of this planning grant is to investigate the function and inhibition of lipid transport mechanisms in Mycobacterium tuberculosis, towards developing more effective anti-TB therapeutics. Agency: Health Now/SUNY Network of Excellence in Health; April 17, 2014 – August 31, 2015. There is no overlap with the current application. P.I. Jessica Seeliger; Co:PI: M. Mahmood Hussain.

“microRNA-30c mimics as potential therapeutic agents to lower plasma lipids & regress atherosclerosis”. The goal of this grant is to find out if miR-30c mimics curtail diet induced hyperlipidemia and atherosclerosis in western diet fed C57Bl6J and *Apoe*<sup>-/-</sup> mice. Agency: Technology Accelerator Fund Class 2014 Fund/Research Foundation of SUNY; September 08, 2014 – February 27, 2015. There is no overlap with the current application. PI: M. Mahmood Hussain.

### Past Research Support

“Molecular mechanisms of chylomicron assembly” The aims are to study the secretion of free and esterified cholesterol by enterocytes. Agency NIH/NIDDK, RO1 DK46900. This grant started in Jan 1995 and had been renewed several times. The last funding period was from 8-1-2007 to 7-31-2013.

### Pending

None

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Girnun, Geoffrey D.</b>	POSITION TITLE <b>Associate Professor</b>		
eRA COMMONS USER NAME GEOFFREY_GIRNUN			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, medical, dental, veterinary, and business training, if applicable)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Iowa, Iowa City, IA	BS	1994	Physiology/Exer. Science
University of Iowa, Iowa City, IA	PhD	1999	Free Radical Radiation Bio

**A. Personal Statement**

Research in my lab is focused on linking fundamental aspects of metabolism and cancer. My research has focused on metabolic regulators and their role in disease. Currently my lab is focused on metabolic alterations in cancer that are driven by specific oncogenic changes. We are also focused on metabolic links underscoring the increase in colon cancer and GI cancer risk in obese and diabetic patients. In particular, we are also interested in how these metabolic changes can be used as biomarkers and in identifying cancer disparities in minority populations. We focus on metabolic regulators driving cancer by promoting metabolic changes associated with cancer as well as specific oncogenes and tumor suppressor genes and the metabolic pathways they control as a means of driving cancer. In addition, we study how metabolic pathways can drive signaling pathways that promote cancer.

**B. Positions and Honors.****Positions and Employment**

1994-1999	Ph.D. Student, Department of Free Radical and Radiation Biology, University of Iowa College of Medicine
1999-2003	Post-doctoral Fellow, Cell/Cancer Biology, Harvard Medical School and Dana-Farber Cancer Institute
2003-2007	Instructor in Cell/Cancer Biology, Harvard Medical School and Dana-Farber Cancer Inst.
2007-2013	Assistant Professor of Biochemistry and Molecular Biology, University of Maryland School of Medicine
2013-present	Associate Professor of Pathology, Stony Brook University School of Medicine
2013-present	Director, Program in Cancer Metabolism, Stony Brook Cancer Center

**Honors and Awards**

2006-2007	Madeline Franchi Ovarian Cancer Fund Award
2005-2007	Claudia Adams Barr Foundation Award (Co-PI)
2003-2008	NIH K01 Award
2001-2003	Individual National Research Service Award, NIDDK
2000-2001	National Research Service Award Trainee, NCI
1998-1999	Carver Medical Research Trust Award, University of Iowa College of Medicine.
1996	Radiation Research Society "Young Investigator" Award. The 44th Annual Radiation Research Society Meeting, Chicago, IL
1994-1998	Scotia Pharmaceuticals Ltd. (UK) Predoctoral Fellowship

**PUBLICATIONS:**

*Selected peer-reviewed publications (in chronological order):*

### **Most relevant to the current application (From list of 26)**

1. Preuss, M., Girnun, G.D., Darby, C., Khoo, N., and Spector, A.A., Robbins, M.E.C. Role of antioxidant enzyme expression in the selective cytotoxic response of glioma cells to  $\gamma$ -linolenic acid supplementation. **Free Rad. Bio. Med.** 28:1143-1156, 2000. PMID: 10832077.
2. Girnun, G.D., Domann, F.E., Moore, S.A., Robbins, M.E. Identification of a functional peroxisome proliferator-activated receptor response element in the rat catalase promoter. **Mol. Endocrinol.** 16:2793-801, 2002. PMID: 12456800.
3. Girnun, G.D., Smith, W.M., Drori, S., Sarraf, P., Mueller, E., Eng, C., Nambiar, P., Rosenberg, D.W., Bronson, R.T., Edelman, W., Kucherlapati, R., Gonzalez, F.J., Spiegelman, B.M. APC-dependent suppression of colon carcinogenesis by PPAR $\gamma$ . **Proc Natl Acad Sci USA.** 99:13771-6, 2002. PMCID: PMC129773.
4. Nambiar, P.R., Girnun, G.D., Lillo, N.A., Guda, K., Whiteley, H.E., Rosenberg, D.W. Preliminary analysis of azoxymethane induced colon tumors in inbred mice commonly used as transgenic/knockout progenitors. **Int. J. Oncol.** 22:145-50, 2003. PMID: 12469197.
5. \*Drori, S., \*Girnun, G.D., Mueller, E., Sarraf, P., Tou, L., Szwaya, J. Shivdasani, R., Spiegelman, B.M. Hic-5 regulates an epithelial program mediated by PPAR $\gamma$ . **Genes Dev.** 19:362-375, 2005. \*equal authorship PMCID: PMC546514.
6. Girnun, G.D., Naseri, E., Vafai, S., Qu, L., Szwaya, J., Bronson, R., Alberta, J., Spiegelman, B.M. Synergy between PPAR $\gamma$  ligands and platinum-based drugs in cancer. **Cancer Cell.** 11:395-406, 2007. PMCID: PMC2564847.
7. \*Girnun, G.D. Chen, L., Silvaggi, J., Drapkin, R., Chirieac, L.R., Padera, R.F., Upadhyay, R., Vafai, S.B., Wiessler, R., Mahmood, U., Naseri, E., Buckley, S., Li, D., Force, J., McNamara, K., Demetri, G., Spiegelman, B.M., \*Wong, K.K. Regression of drug-resistant lung cancer by the combination of rosiglitazone and carboplatin. **Clin. Cancer Res.** 14:6478-6486, 2008. PMCID: PMC2696122. \*Co-corresponding author
8. Girnun, G.D. PPAR $\gamma$ : A new independent marker for colorectal survival. **Gastroenterology.** 136:1157-1160, 2009. PMID: 19236969.
9. Souza, D.R., Pierce, A., Girnun, G., Passaniti, A. Glucose metabolism, transcriptional regulation and angiogenesis. 2009 **Current Topics Biochem. Res.** 11, 41-55.
10. Bhalla, K., Hwang, B.J., Dewi, R., Twaddell, W., Girnun, G.D. The metabolic coactivator PGC1 $\alpha$  promotes tumor growth by coordinating a gene expression program driving de novo fatty acid synthesis. **Cancer Res.** 71:6888-6898, 2011, PMID21914785
11. Bhalla, K, Hwang, B., Dewi, R., Choi, J-H., Dewi, R., Ou, L., Twaddell, W., Mclenithan, J., Voronkov, M., Stock, M., Perez, E., Stock, J., Pozharskiy, E., Girnun, G.D. N-Acetyl Farnesyl Cysteine is a novel class of PPAR $\gamma$  ligand with partial and full agonist activity *in vitro and in vivo*. **J. Biol Chem.** 286: 41626-416335, 2011 PMID: 21979952
12. Bhalla, K, Hwang, B., Dewi, R., Twaddell, W., Girnun, G.D. Metformin prevents hepatocellular carcinoma by antagonizing hepatic lipogenesis. **Cancer Prev Res.** 5: 544-552, 2012, PMID:22467080
13. Girnun, G.D. The diverse role of the PPAR $\gamma$  Coactivator-1 family of transcriptional coactivators. **Seminars in Cell and Developmental Biology. Cancer Cell Metabolism Issue.** 23:381-384, 2012, PMID: 22285815
14. Mehrabian, Z, Clerc, P, Carey, G, Michael Wei, M., Hwang, H., Girnun, G.D., Chen, H., Martin, S.S., Polster, B.M. Rapid detection of a "primed for death" state of BCL-2 dependence in cells using microplate-based respirometry. **PloS One**, 7:e42487, 2012, PMID:22880001
15. Vazquez, F., Lim, J.H., Chin, H., Girnun, G.D., Widlund, H.R., Spiegelman, B.M., Puigserver. The transcriptional coactivator PGC1 $\alpha$  defines a subset of human melanoma tumors with increased mitochondrial capacity and resistance to oxidative stress. **Cancer Cell**, 23:287-301, 2013.
16. Singh, A., Happel, C., Manna, S.K., Acquah-Mensah, G., Carratero, J., Kumar, S., Nasipuri, P., Krausz, K.W., Dewi, D, Boros, L.G., Gonzalez, F.J., Gabrielson, E., Wong, K.K., Girnun, G.D.\*, Biswal, S\*. Nrf2 regulates miR-1 and miR-206 to drive tumorigenesis. **J. Clin. Invest.** 123: 2921-2934, 2013. \*Co-corresponding author
17. Choe, C. Chumsri, S., Jones, L., Bhandary, L., Zhao, X.F., Lu, S., Goloubeva, O.G. Polster, B.M., Fiskum, G.M., Girnun, G.D. , Passaniti, A. Control of breast cancer metabolism and differentiation by the RUNX2 oncogene through modulation of SIRT6 suppressor gene expression. **Oncogene, Accepted pending revisions.**

18. Liu, WJ., Bhalla, K., Naseri, E., Hwang, B., Vafai, S., Anders, L., Sicinski, P., Girnun, G.D. Cyclin D1 suppresses gluconeogenesis via inhibition of PGC1alpha. **Diabetes**. 63:3266-78, 2014.

## D. Research Support

### Ongoing Research Support

1R01CA169919-01 Girnun, (PI) 07/09/2012-04/30/2017  
NIH/NCI \$211,248 3 cal

Title: Metabolic control of hepatocellular carcinoma by PGC1alpha

These studies are designed to determine the mechanisms by which PGC1alpha promotes liver cancer. In addition, they designed to determine whether PGC1 is a key mediator explaining increased liver cancer in diabetes.

1R01CA140492-01A1 (Co-I, S. Biswal-PI) 01/01/2010-12/31/2015  
NIH/NCI \$202,700 0.6 cal

Title: Regulation of tumorigenesis and therapeutic resistance by NRF2 in lung cancer. These studies are seeking to define the role of Nrf2 in lung cancer. Dr. Girnuns role is leading these studies in the aspects of metabolism and cancer. No overlap

VA Merit Award (Co-I, Passiniti-PI) 04/13/2013-03/31/2017  
Title: Transcriptional regulation of tumor growth \$263,000 0.6 cal

Start up funds (Girnun, PI)  
Office of the Vice president for Research and Cancer Center

### **Past support**

1R01CA169919-01 Girnun (PI) 09/01/2013-04/30/2014  
NIH/NCI- No cost extension 0.3 cal

Supplement- Collaborative Activities to Promote Metabolomics Research  
Metabolic control of hepatocellular carcinoma by PGC1alpha

KG081400 Girnun (PI) 08/01/08-07/31/2011

Susan G. Komen Foundation Career Catalyst Development Award

Title: Bioenergetic Control of breast cancer growth by the transcriptional activator PGC1 $\alpha$ . The goal of this project is to determine the role of PGC1 $\alpha$  in breast cancer.

## BIOGRAPHICAL SKETCH

NAME & CONTACT INFORMATION Michael A Frohman 438 CMM 631-632-1476		POSITION TITLE Professor and Chair of Pharmacology Director, Medical Scientist Training Program	
eRA COMMONS USER NAME & E-mail address mfrohman michael.frohman@stonybrook.edu			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
U. of Michigan; Ann Arbor	B.S. High Honors	1978	Chemistry & Cell & Molecular Biology
U. of Pennsylvania; Philadelphia	M.D., PhD.	1985	Medicine. Immunology
U. of Cal. at San Francisco	Postdoc	1986-92	Mammalian Developmental Biology

### A. Personal Statement:

My laboratory cloned the mammalian family of lipid-signaling Phospholipase D genes (PLD1 in 1995, PLD2 in 1997, and MitoPLD in 2006) and has worked on them for the past 18 years while publishing nearly 100 peer-reviewed articles and reviews on PLD and other lipid signaling topics with additional ones in submission. PLD superfamily members are involved in many physiological and pathophysiological settings including immune defenses, cancer, neurodegenerative disease, diabetes, cardiovascular disease, and fertility. Among other approaches, we have recently been generating and publishing findings with mice lacking each of the PLD isoforms, and have uncovered a number of fascinating stories with human health relevance. Recent work has included exploring the potential of using a Phospholipase D small molecule inhibitor as a therapeutic in stroke, Alzheimer's Disease, cardiovascular disease and cancer progression settings.

I have been the Director of the Medical Scientist Training Program (MSTP, MD-PhD) at SBU for 13 years, renewing the T32 training grant three times. I am a graduate myself of an MSTP (U. Penn.), have been continuously funded by NIH for my research since the beginning of my faculty position in 1992, and have trained more than 50 students and fellows, approximately 20% of whom have been URM trainees. I have been an external reviewer of other Graduate and MD-PhD training programs since 2006 and have participated in study section reviews of MSTP T32 training grants and individual F-series NRSAs.

Many of the graduate student trainees in my lab have gone on to excellent research career paths, including URM ones:

Yeku Oladapo (Medgar Evers Coll.), 2006-2010; SBU MSTP (Pharmacology Graduate Program); U. Pitt. Int. Med.; Mt. Sinai Heme-Onc fellowship

Mary Osisami (SBU undergrad), 200—2012; Genetics Graduate Program (current: post-doc, University of Michigan)

Akua Bonsra (SBU undergrad), 2005 – 2010; Pharmacology Graduate Program; Regulatory Affairs Specialist at Technical Resources International, Inc

### B. Positions and Honors

#### Positions:

1992-98; 98-03 Assistant & Associate Professor, Stony Brook University, Dept. Pharmacology  
 1995 – 2003 Director, Medical Pharmacology course, SBU School of Medicine  
 2002 - Director, Molecular Cloning Facility Core, Stony Brook University  
 2003 - Professor, Stony Brook University, Dept. Pharmacology  
 2003 - Director, Medical Scientist Training Program (MD/PhD, MSTP) at Stony Brook University  
 2007 - Chair, Department of Pharmacology

#### Honors and Professional Activities:

1977, 78 Michael Reese, U. Michigan Medical Student Summer Research Scholarship  
 1979-1985 Scholarship: NIH Medical Scientist Training Program

1984	Roy G. William Award
1986, 89	Post-doc Fellowships: American Cancer Society, Leukemia Society Senior Fellowship
1993	Basil O'Connor Young Investigator Award, March of Dimes
1994, 95, 96	NIH Cell Biology 1, HED-2 Study Section Special Reviewer
1998-2003	Editorial Board, Journal of Biological Chemistry
1998, 2000	Co-Chair, FASEB, ASPET Meetings on Phospholipases, PLD (Vermont, Boston)
1999 - 2003	NIH Special Emphasis Panel Study Section Ad-hoc Reviewer (ZRG1 SSS-Y 01)
2001	Chair, FASEB Meeting on Phospholipase D (Colorado)
2002, 2006, 2009	NIH P01 Special Emphasis Reviewer; NIH NRSA study section adhoc review panel
2004- 2007	Editorial Board, Journal of Endocrinology
2006-	External Advisory Board, Penn State Medical Scientist Training Program
2007-2008	Guest Co-Editor, Special issue on Phospholipase D in BBA Lipids
2007-	Editorial Boards, J. Functional Develop & Embryology; Molecular & Cellular Pharmacology
2009	NIH MPP Study Section Ad-hoc Reviewer
2010	External reviewer, Molecular Medicine Graduate Program, Med. Coll. Of Georgia
2010	Platform speaker, GPCR 2010 symposium, Helsinki, Finland
2011	Keynote speaker, National conference for MD-PhD training, Gwangju, South Korea
2012 -	Review Editorial Board of Frontiers in Mitochondrial Research
2012	NIH T32 Study Section Ad-hoc Reviewer for MSTP applications (February and June)
2013 -	Councilor, <i>Association of Medical School Pharmacology Chairs (AMSPC)</i>
2014 -	Editorial Board, " <i>Handbook of Experimental Pharmacology</i> "
2014 -	Advisory board, DO/PhD program, New York Institute of Technology

### C. Selected Peer-reviewed Publications (Selected from 184 total publications); h-index 61

#### Most relevant to the current application

- Choi, S.-Y., Huang, P., Chan, D.C., and Frohman, M.A. (2006) A common signaling lipid requirement for Mfn-mediated mitochondrial fusion and SNARE-regulated exocytosis. ***Nature Cell Biology*** 8:1255-62.
- Zhao, C., Du, G., Skowronek, K., Frohman, M.A., and Bar-Sagi, D. (2007) Phospholipase D2-generated PA couples EGFR stimulation to Ras activation by Sos. ***Nature Cell Biology***, 9:707-12. PMID: 17486115
- Yang, J.-S. et al. (2008) COPI vesicle fission: a role for phosphatidic acid and insight into Golgi maintenance. ***Nature Cell Biology***, 10:1146-53. PMID: 18776900
- Su, W., Yeku, O., Olepu, S., **Genna, A.**, Park, J.-S., Ren, H., Du, G., Gelb, M.H., Morris, A.J., and Frohman, M.A. (2009) FIPI, a PLD pharmacological inhibitor that alters cell spreading and inhibits chemotaxis. ***Molecular Pharmacology*** 75:437-46. PMID: 19064628
- Nishikimi et al. (2009) Sequential Regulation of DOCK2 Dynamics by Two Phospholipids during Neutrophil Chemotaxis. ***Science***, 324:384-7. PMID: 19325080
- Tsukahara et al. (2010) The novel second messenger Cyclic Phosphatidic Acid Negatively Regulates the Nuclear Hormone Receptor PPAR $\gamma$ . ***Molecular Cell***, 39:421-32.
- Elvers, M., Stegner, D., Hagedorn, I., Kleinschnitz, C., Braun, A., Kuijpers, M.E.J., Boesl, M., Chen, Q., Heemskerk, J.W.M., Stoll, G., Frohman, M.A., and Nieswandt, B. (2010) Impaired integrin  $\alpha$ IIb $\beta$ 3 activation and shear-dependent thrombus formation in mice lacking phospholipase D1. ***Science Signaling***, 3:1-10.
- Dall'Armi, C et al. (2010) The Phospholipase D1 Pathway Modulates Macroautophagy. ***Nature Communications***, 1:142-152.
- Huang, H., Gao, Q., Peng, X.X., Choi, S.-Y., **Sarma, K.**, Ren, H., Morris, A.J., and Frohman, M.A. (2011) piRNA-associated germline nuage formation and spermatogenesis require MitoPLD pro-fusogenic mitochondrial-surface lipid signaling. ***Developmental Cell***, 20:376-387.
- Huang, P., Yeku, O., Zong, H., Tsang, P., Su, W., Xu, X., Teng, S., Osisami, M., Kanaho, Y., Pessin, J.E., and Frohman, M.A. (2011) Phosphatidylinositol-4-Phosphate-5-Kinase  $\square$  Deficiency Alters Dynamics of Glucose-Stimulated Insulin Release to Improve Glucohomeostasis and Decrease Obesity in Mice. ***Diabetes***, 60:454-63.

Chen, Q., Hongu, T., Sato, T., Zhang, Y., Ali, W., Cavallo, J.-A., van der Velden, A., Tian, H., Di Paolo, G., Nieswandt, B., Kanaho, Y., and Frohman, M.A. (2012) Key roles for the lipid signaling enzyme PLD1 in the tumor microenvironment during tumor angiogenesis and metastasis. **Science Signaling**, 5:ra79.

- with accompanying Podcast in *Science Signaling*; highlighted in **Nature Cancer Reviews** (2013) and in the *Cancer Discovery Research Watch* by the American Assoc. for Cancer Research (Nov. 15<sup>th</sup>, 2012).

Osisami, M., Ali, W. and Frohman, M.A. A role for Phospholipase D3 in myotube formation. (2012). **PLoS One**, 7(3): e33341.

Stegner, D., Thielmann, I., Kraft, P., Frohman, M.A., Stoll, G., and Nieswandt, B. (2013) Pharmacological inhibition of phospholipase D protects mice from occlusive thrombus formation and ischemic stroke. **Arteriosclerosis, Thrombosis, and Vascular Biology**, 33:2212-7.

Li, S. et al.. (2013) High throughput sequencing analysis of natural regulatory and conventional T cell receptor repertoires during human H1N1 challenge. **Nature Communications**, 4:2333.

Akiyama, M., Hasegawa, H., Hongu, T., Frohman, M.A., Harada, A., Sakagami, H., and Kanaho, Y. (2014) Trans-regulation of oligodendrocyte myelination by neurons through small GTPase Arf6-regulated secretion of fibroblast growth factor-2. **Nature Communications**, 5:4744.

Mallipattu SK, Horne SJ, D'Agati V, Narla G, Liu R, Frohman MA, Dickman K, Chen EY, Ma'ayan A, Bialkowska AB, Ghaleb AM, Nandan MO, Jain MK, Daehn I, Chuang PY, Yang VW, He JC. (2015) Krüppel-like factor 6 regulates mitochondrial function in the kidney. **J. Clinical Investigation**, 125:1347-61.

#### D. RESEARCH SUPPORT

<b>R01</b> (PI, Frohman)	9/2012 - 8/2016
NIH GM100109 MitoPLD and RNA processing on the mitochondrial surface	
<b>R01</b> (PI, Frohman)	9/1/09 - 8/31/18
NIH GM084251	
Lipid-signaling pathways regulating mitochondrial morphology, energetics, and movement	
<b>Carol Baldwin Breast Cancer Award</b>	7/2013 – 6/2015
Inhibition of PLD1 as a therapeutic approach in breast cancer	

#### Mentored funding

NIH <b>NRSA</b> F31 Predoctoral fellowship to Rochelle Nelson	6/1/13 – 5/31/16
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Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Jian Cao	POSITION TITLE		
eRA COMMONS USER NAME (credential, e.g., agency login)	Professor of Medicine		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
School of Medicine, Zhengzhou University, Henan, China	M.D.	07/85	Medicine
Hospital Attached to Zhengzhou University, Henan, China	Intern	07/86	Medicine
Peking Union Medical College, Tsinghua University, Beijing, China	M.S.	07/92	Experimental Pathology
Cancer Institute, Kanazawa University, Kanazawa, Japan	Postdoctoral	05/95	Molecular Biology of Cancer
Stony Brook University, Stony Brook, NY	Postdoctoral	05/98	Cellular Biology of Cancer

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

**A. Personal Statement**

Dr. Cao is a Medical Scientist whose career began shortly after receiving his medical doctoral degree at Zhengzhou University School of Medicine (Henan Medical University), China. His interest in cancer research began during his training in experimental pathology in Peking Union Medical College, Tsinghua University (Chinese Academy of Medical Sciences) in Beijing, China, where he received his Master Degree of Sciences. Dr. Cao's research background was further strengthened in the field of molecular and cellular biology of cancer during his postdoctoral training in the laboratories of Dr. M. Seiki in Japan and Dr. S. Zucker in New York. He was among the first scientists to discover the membrane type 1-matrix metalloproteinase (MT1-MMP) and Cell Migration-inducing Protein (CEMIP) and demonstrated that these cancer metastasis-driving genes are targetable molecules aimed at preventing cancer dissemination. Dr. Cao joined the faculty at Stony Brook University in 1998 as an Assistant Professor, was promoted to Associate Professor in 2008 and then full Professor in 2014. His work at Stony Brook University led to: 1) the demonstration of the role of MT1-MMP in early cancer dissemination; 2) the discovery of an alternative approach targeting specific MMPs; 3) the identification of a novel surrogate marker in cancer cell migration/invasion; and 4) the development of a powerful screening tool for anti-cancer drug discovery using a three-dimensional cell culture system. His current research interests involve studying three broad aspects of cancer metastasis: 1) to better understand the mechanism of cancer invasion and metastasis; 2) to develop novel tools for early cancer diagnosis and prognosis; and 3) to identify inhibitors of cancer dissemination. Dr. Cao's long-term goal is to develop drugs to prevent metastasis.

**B. Positions and Honors****Positions and Employment**

1986-1989	Lecturer in Pathology, School of Medicine, Henan University, Henan, China
1998-2009	Assistant Professor of Medicine, Stony Brook University, Stony Brook, NY
2005-present	Member, Institute of Chemical Biology & Drug Discovery (ICB&DD)/Stony Brook University
2008-present	Member, Molecular & Cellular Biology Graduate Program/Stony Brook University
2008-present	Member, Molecular & Cellular Pharmacology Graduate Program/Stony Brook University
2008-present	Member, Molecular Genetics Graduate Program/Stony Brook University
2008-present	Assistant Professor of Pathology, Stony Brook University, Stony Brook, NY
2009-2014	Associate Professor of Medicine, Stony Brook University, Stony Brook, NY
2011-present	Member, Chemical Biology Training Program/Stony Brook University
2014-present	Professor of Medicine, Stony Brook University, Stony Brook, NY

Program Director/Principal Investigator (Last, First, Middle):

**Other Experience and Professional Memberships**

1996-present	Member, American Association for Cancer Research (AACR)
2005-2006	Komen Breast Cancer Foundation, Tumor Biology and Cell Biology
2006-2007	Komen Breast Cancer Foundation, Postdoctoral Fellowship Committee
2006	The Israel Science Foundation (Ad hoc)
2008-2009	DOD Breast Cancer Research Program (BCRP) IDEA and Synergistic IDEA Awards
2009-2010	DOD Breast Cancer Research Program (BCRP) Concept Award/Pathobiology-1
2010-2011	DOD Breast Cancer Research Program (BCRP) Concept Award/Pathobiology-3
2010	National Science Foundation (NSF), Chemistry of Life Processes (CLP) Program
2011	DOD Breast Cancer Research Program (BCRP) Postdoctoral Fellowship Award
2012	DOD Prostate Cancer Research Program (PCRP) Idea Development Award, Pathobiology-2
2012	DOD Prostate Cancer Research Program (PCRP) Idea Development Award, Pathobiology-1(Ad hoc)
2012	DMP Study Section, NIH
2012	VA Oncology Merit Review Panel
2013	DMP Study Section, NIH
2013	Breast Cancer Training-PBY peer review panel
2013	The Israel Science Foundation (Ad hoc)
2013	Carol M. Baldwin Breast Cancer Foundation
2012	VA Oncology Merit Review Panel
2013	DOD Prostate Cancer Research Program (PCRP)-Cell Biology-1
2013	2014 State University of New York Collaboration Fund Panel-3 Chemistry
2014	DOD Breast Cancer Training-PBY peer review panel
2014	NIH Director's Early Independence Award peer review panel
2014	DOD Breast Cancer Research Program_ Breakthrough Award peer review panel
2014	DMP Study Section, NIH
2014	VA Oncology Merit Review Panel
2015	DOD Breast Cancer Research Program_ Breakthrough Award peer review panel
2012-present	Academic Editor: PLoS ONE, The Public Library of Science
2012-present	Member, Editorial Board: Journal of Cancer Research & Therapy, NobleResearch Publisher
2012-present	Managing Editor, Frontiers in Bioscience
2012-present	Member, Editorial Board: Dataset Papers in Biology, Hindawi Publishing Corporation
2012-present	Member, Editorial Board: International Journal of Chronic Diseases, Hindawi Publishing Corporation
2013-present	Member, Editorial Advisory Board, Current Cancer Drug Targets, Bentham Science Publishers
2006-2008	Member, Subcommittee on Animal Studies (IACUC) of VA Hospital, Northport, NY
2008-present	Serve as an interviewer for recruiting graduate students for MCB, Genetics, Pharmacology, and Medical Scientist Training Program (M.D./Ph.D.), Stony Brook University
2008-present	Member/co-chair, The Admissions Committee for the Molecular and Cell Biology and Genetics Programs/Stony Brook University
2009-2010	Member of Undergraduate Council of the University Senate, Stony Brook University
2012-present	Executive Core Oversight Committee, School of Medicine, Stony Brook University
2012-2015	Central Microscopy Imaging Center Core Advisory Committee, School of Medicine, Stony Brook University
2012-present	Member of Graduate and Research Committee, University Faculty Senate of the State University of New York (SUNY System)
2012-present	Member of the Department of Medicine's Research Committee, Stony Brook University

**Honors:**

1982-1986	Scholarship to School of Medicine, Zhengzhou University, Henan, China
1982-1986	Distinguished Graduate Student Award, School of Medicine, Zhengzhou University, Henan, China
1993-1994	Research Fellowship award, Ministry of Education, Science, and Culture of Japan
1997-1998	Research Fellowship award, American Heart Association
1998	AACR-Bristol-Myers Squibb Young Investigator Award, New Orleans, LA

Program Director/Principal Investigator (Last, First, Middle):

1998-2001 Postdoctoral Traineeship award, US Army Medical Research and Materiel Command  
 2001 American Association for Cancer Research Scholar-in-Training Award, New Orleans, LA  
 2001 Gordon Research Conference-Matrix Metalloproteinases travel award, Italy  
 2001-2004 Scientist Development Grant award, the American Heart Association  
 2001-2004 New Investigator Award by US Army Medical Research and Materiel Command (PCRP01)  
 2002 American Association for Cancer Research, Scholars in Cancer Research, San Francisco, CA  
 2014 Basic Science Award, Dept. Of Medicine, Stony Brook University

**C. Selected Peer-reviewed Publications (Selected from 55 peer-reviewed publications)**Most relevant to the current application

1. **Cao J**, Kozarekar P, Pavlake M, Chiarelli C, Bahou WF, Zucker S. (2004). Distinct roles for the catalytic and hemopexin domains of membrane type 1-matrix metalloproteinase metalloproteinase in substrate degradation and cell migration. **J Biol Chem**. 279(14):14129-39. PMID: 14729674
2. **J. Cao**, M. Hymowitz, C. Conner, W. Bahou and S. Zucker (2000). The propeptide domain of membrane type 1-matrix metalloproteinase acts as an intramolecular chaperon when expressed in trans with the mature sequence in COS-1 cells. **J.Biol.Chem.**, Vol.275:29648-29653, PMID:10889191
3. **Cao J**, Chiarelli C, Kozarekar P, and Adler HL. (2005). MT1-MMP Promotes Human Prostate Cancer Invasion and Metastasis. **Thromb Haemost**. 93:770-8, PMID: 15841326
4. **Cao J**, Rehemtulla A, Pavlaki M, Kozarekar P, Chiarelli C. (2005). Furin directly cleaves proMMP-2 in the trans-Golgi network resulting in a non-functioning proteinase. **J Biol Chem**. 280:10974-80. PMID: 15637056
5. **Cao J**, Chiarelli C, Richman O, Zarrabi K, Kozarekar P, Zucker S. (2008). MT1-MMP induces epithelial-to-mesenchymal transition (EMT) in prostate cancer. **J Biol Chem**. 283(10):6232-40. PMID: 18174174
6. Antoine Dufour, Nicole Sampson, Stanley Zucker and **Jian Cao** (2008). Role of the Hemopexin Domain of Matrix Metalloproteinases in Cell Migration, **J Cell Physiol**. 217(3):643-51. PMID: 18636552
7. Dufour A, Zucker S, Sampson NS, Kuscus C, **Cao J**. (2010). Role of matrix metalloproteinase-9 (MMP-9) dimers in cell migration: design of inhibitory peptides\* **J. Biol. Chem.**, 12;285(46):35944-56. PMID: 20837483 \* This work was featured in F1000Prime, Post-publication Peer Review, Jan. 2011
8. Antoine Dufour, Nicole S. Sampson, Jian Li, Cem Kuscus, Robert Rizzo, Jennifer L. DeLeon, Jizu Zhi, Nadia Jaber, Eric Liu, Stanley Zucker and **Jian Cao** (2011). Small Molecule Anti-Cancer Compounds Selectively Target the Hemopexin Domain of Matrix Metalloproteinase-9 (MMP-9)\*, **Cancer Res**. 71(14):4977-88. PMID:21646471  
 \* This work was featured in **SciBX** (JUNE 23, 2011 • VOLUME 4 / NUMBER 25), a publishing collaboration between **BioCentury** Publications, Inc. and **Nature** Publishing Group.
9. Kevin Zarrabi, Antoine Dufour, Jian Li, Cem Kuscus, Jizu Zhi, Youjun Hu, Nicole S. Sampson, Stanley Zucker, and **Jian Cao** (2011). Inhibition of matrix metalloproteinase-14 (MMP-14)-mediated cancer cell migration\* **J. Biol. Chem**. 286(38):33167-77. PMID:21795678  
 \* This work was featured in F1000Prime, Post-publication Peer Review, Aug. 2011
10. Nguyen HL, Zucker S, Zarrabi K, Kadam P, Schmidt C, **Cao J** (2011). Oxidative stress and prostate cancer progression are elicited by membrane-type 1 matrix metalloproteinase. **Mol Cancer Res**. 9(10):1305-18. PMID: 21849471
11. Li J, Zucker S, Pulkoski-Gross A, Kuscus C, Karaayvaz M, Ju J, Yao H, Song E, **Cao J**. (2012) Conversion of Stationary to Invasive Tumor Initiating Cells (TICs): Role of Hypoxia in Membrane Type 1-Matrix Metalloproteinase (MT1-MMP) Trafficking. **PLoS One** 7(6):e38403; PMID:22679501.  
 \* This work was featured in Faculty of 1000, Post-publication Peer Review, June 2012
12. Cem Kuscus, Nikki Evensen, Deborah Kim, You-Jun Hu, Stanley Zucker, and **Jian Cao** (2012):Transcriptional and Epigenetic Regulation of KIAA1199 Gene Expression In Human Breast Cancer \*. **PLoS One** 2012;7(9):e44661, PMID 22970280.  
 \* This work was featured in World Biomedical [ISSN: 2328-0166]
13. Nikki A Evensen, Cem Kuscus, Kevin Zarrabi, Antoine Dufour, Pournima Kadam, You-jun Hu, Ashleigh Pulkoski-Gross, Hoang-Lan Nguyen, Wadie F. Bahou, Stanley Zucker, and **Jian Cao** (2013) Unraveling the Role of KIAA1199, A Novel Endoplasmic Reticulum Protein in Cancer Cell Migration, **J Natl Cancer Inst**. 105(18):1402-16. PMID: 23990668
14. Nikki A. Evensen, Jian Li, Jie Yang, Xiaojun Yu, Nicole S. Sampson, Stanley Zucker, and **Jian Cao** (2013)

Program Director/Principal Investigator (Last, First, Middle):

Development of a High-Throughput Three-Dimensional Invasion Assay for Anti-Cancer Drug Discovery, **PLoS One** December 2013; 8 (12):e82811. PMID: 24349367

15. Pulkoski-Gross AE, Li J, Zheng C, Li Y, Ouyang N, Rigas B, Zucker S, **Cao J** Repurposing the Anti-psychotic Trifluoperazine as an Anti-metastasis Agent. **Mol Pharmacol**. 2014 Dec 31. PMID: 25552486 [Epub ahead of print]

#### D. Research Support

##### Ongoing Research Support

1R01CA166936-01 (NIH/NCI) Cao (PI) 04/02/2012- 03/30/2017

Title: Integrating Anti-invasive and Anti-growth Therapies Targeting Cancer Metastasis

The major goals of this proposal are to understand the interplay between tumor initiating cells (TICs) and their microenvironment during the transition to invasion and metastasis, as well as to develop a novel treatment reagent to specifically induce invasive TIC death in a preclinical setting.

##### Completed Research Projects for the Past Three Years

\* Carol M. Baldwin Breast Cancer Research Award Cao (PI) 08/01/12-07/31/14

Title: A Novel 3-Dimensional High-Throughput Assay for Targeting Invasive Breast Cancer Cells

The goal of this proposal is to develop a phenotypic screening assay that monitors breast cancer cell invasion in a 3-D environment.

\* R01 CA113553-05 (NCI/NIH) Cao (PI) 04/01/2006- 03/31/2012

Title: Targeting the PEX Domain of MT1-MMP: Novel Cancer Therapy

The major goals of this proposal are to examine the role of MT1-MMP in early stage of cancer invasion and develop specific inhibitors against the hemopexin (PEX) domain of MT1-MMP.

\* R01 CA113553-04S1 (NCI/NIH), Cao (PI, Mentor) 08/01/07- 03/31/11

Title: Targeting the PEX Domain of MT1-MMP: Novel Cancer Therapy This supplemental grant supports Dr. Nguyen's Postdoctoral Traineeship under the PI's R01 grant.

\* Centocor, Inc. Collaborative Award Cao (PI) 09/01/05–12/31/10

The purpose of this award is to improve academic-industry collaboration for evaluation the effect of Centocor's Extracellular Matrix Metalloproteinase Inducer (EMMPRIN) antibody on an orthotopic breast cancer animal model.

\* DOD BCRP Concept Award (W81XWH1010415) Cao (PI) 09/01/10 - 10/31/12

Title: Development of a Novel Cell-Based, High-Throughput Screening Assay for Anti- metastatic Breast Cancer Stem Cell Drug Discovery

The primary goal of this pilot study is to develop a novel cell-based high throughput screening (HTS) assay which allows for the simultaneous determination of metastatic breast cancer stem cell (CSC) migratory ability as well as proteolytic activity.

\* DOD BCRP Concept Award (W81XWH0910358) Shi and Cao (PIs) 09/01/09 - 10/31/11

Title: Detection of Circulating Cancer Cells Using Nano Acoustic Waves

The aim of this proposal is to detect circulating tumor cells (CTCs) in blood of patients with breast cancer using nano acoustic wave (NAW) technology. This is a joint effort between Stony Brook University and Stevens Institute of Technology (NJ).

\* Carol M. Baldwin Breast Cancer Research Award Cao (PI) 11/01/09-10/31/11

Title: Targeting Metastatic Breast Cancer Stem Cell Invasion

The goal of this application is to identify specific inhibitory hits targeting breast cancer stem cells with invasive properties by screening the compound libraries using our 3D invasion HTS assay.

\* Organomed Corporation. Collaborative Award Cao (PI) 06/18/10–12/31/11

Title: Evaluation of Novel Synthetic Compounds Targeting Cancer Cell Proliferation

The purpose of this award is to improve academic-industry collaboration for evaluation the effect of newly generated synthetic compounds inducing cancer cell apoptosis. The compounds are being examined using in vitro and in vivo cancer models.

\* Stony Brook University-Brookhaven National Lab Seed Grant Cao, Sampson, and Fowler (PIs) 09/01/10-08/31/11

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Scharer, Orlando D.</b>	POSITION TITLE Professor of Pharmacological Sciences and Chemistry		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>OSHARER</b>			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
ETH, Zürich, Switzerland	Diplom	1991	Chemistry
Harvard University, Cambridge, MA	PhD	1996	Chemistry
Erasmus University, Rotterdam, Netherlands	Postdoc	1996-99	Genetics/Biochemistry

### A. PERSONAL STATEMENT

Research in my laboratory combines organic chemistry, biochemistry and molecular and cellular biology to study the mechanism of mammalian nucleotide excision repair (NER) and interstrand crosslink (ICL) repair. We are interested in two fundamental questions: 1) What are the molecular mechanisms by which DNA repair pathways counteract carcinogenesis and 2) How might we exploit our understanding of DNA repair pathways to improve cancer chemotherapy. Our laboratory has extensive experience in the synthesis of site-specific DNA adducts, including interstrand crosslinks (ICLs) formed by cisplatin, nitrogen mustards and chloro ethyl nitroso ureas as well as adducts formed by environmental mutagens such as AAF. We have used such substrates extensively for the study of the NER and ICL repair pathways. Our studies of the NER pathway have yielded a new model of how the activity of the two endonucleases ERCC1-XPF and XPG are regulated and coordinated to ensure smooth progression through the NER pathway. Our studies of ERCC1-XPF have furthermore provided a molecular bases for how mutations in this heterodimer can lead to three genetic disorders: xeroderma pigmentosum, Fanconi anemia and the progeria XFE syndrome. Our studies using our synthetic ICLs have shown how these lesions interact with translesion synthesis polymerases and yielded important insights into the mechanisms of replication-dependent and -independent ICLs. To date I have trained 18 graduate students and 4 postdocs and numerous undergraduates and rotation students in my laboratory.

### B. POSITION AND HONORS

#### Positions and Employment

1999-2005 Group Leader, START Fellow at the Institute of Molecular Cancer Research, University of Zürich, Switzerland.

2002-2005 Lecturer, Department of Chemistry, ETH Zurich, Switzerland

2005-2011 Associate Professor (with tenure) of Pharmacological Sciences and Chemistry, Stony Brook University, NY

2005- Member, Institute of Chemical Biology and Drug Discovery, Stony Brook University, NY

2005- Member, Molecular and Cellular Biology and Biochemistry and Biophysics Graduate Programs, Stony Brook University, NY

2011- Professor of Pharmacological Sciences and Chemistry, Stony Brook University, NY

#### Awards

1996-1997 Post doctoral fellow of the Swiss National Science Foundation

1997-1999 Human Frontier Science Program long-term postdoctoral fellow

1997 Awarded EMBO postdoctoral fellowship

1999-2005 START fellow of the Swiss National Science Foundation

2001 EMBO Young Investigator Award

2005 NYSTAR Faculty Development Award

**Selected Professional activities**

2015	Chair, Mammalian DNA Repair Gordon Research Conference
2013	Vice Chair, Mammalian DNA Repair Gordon Research Conference
2013-	Contributing member; <i>Faculty of 1000</i>
2012-	Editorial Board, Environ Mol Mutagen
2011	Guest Editor for special issue of DNA Repair on Nucleotide Excision Repair
2014	NIH CE study section, chair
2012-2013	NIH CE study section, co-chair
2009-2014	NIH CE study section, regular member
2008-2009	NIH CE study section, Ad hoc member
2008	NCI Molecular Oncology P01 SEP member
2001-	External Reviewer for NSF, HFSP, ERC, EMBO, AICR, Cancer Research UK, Wellcome Trust, Research Fondation, Research Cooperation, A*STAR, Swiss Cancer League
2000-	Ad hoc reviewer for >40 Journals, including Science, Nature, Nat Cell Biol, Nat Struct Mol Biol, Nat Chem Biol, Cell, Mol Cell, Genes Dev, EMBO J, PNAS, PLoS Biology, MCB, Angew Chem, JOC, Org Lett.

**C. SELECT RECENT PEER-REVIEWED PUBLICATIONS** (from a total of 71, h-index = 32)

1. Mukherjee S, Guainazzi A, **Schärer OD** (2014) Synthesis of structurally diverse DNA interstrand crosslinks using postsynthetic reductive amination. **Nucleic Acids Res**, 42, 7429-7435 PMCID: PMC4066762.
2. Hodskinson MR, Silhan J, Crossan GP, Garaycochea JI, Mukherjee S, **Schärer OD**, Patel KJ (2014) Mouse Slx4 is a tumour suppressor that stimulates the activity of the nuclease Xpf-Ercc1 in DNA crosslink repair. **Mol Cell**, 54, 472-484. PMCID: PMC4017094.
3. Guillemette S, Branagan A, Peng M, Dhruva A, **Schärer OD**, Cantor SB (2014) FANCD1 localization by mismatch repair is vital to maintain genomic integrity after UV irradiation. **Cancer Res**, 74, 932-944. PMCID: in progress.
4. Bogliolo M, Schuster B, Stoepker C, Derkunt B, Su Y, Raams A, Trujillo JP, Minguillón J, Ramírez MJ, Pujol R, Casado JA, Baños R, Rio P, Knies K, Zúñiga S, Benítez J, Bueren JA, Jaspers NGJ, **Schärer OD**, Winter JP, Schindler D, Surrallés J (2013) Mutations in ERCC4, encoding the DNA-repair endonuclease XPF, cause Fanconi anemia. **Am J Hum Genet**, 92, 800-806. PMCID: PMC3644630.
5. Su Y, Orelli B, Madireddy A, Niedernhofer LJ, **Schärer OD** (2012) Multiple domains of ERCC1-XPF contribute to DNA binding in nucleotide excision repair **J Biol Chem**, 287, 21846-21855. PMCID: PMC3381147.
6. Enoiu M, Jiricny J, **Schärer OD** (2012) Repair of cisplatin-induced DNA interstrand crosslinks by a replication-independent pathway involving transcription-coupled repair and translesion polymerases. **Nucl Acids Res**, 40, 8593-8964. PMCID: PMC3467066.
7. Enoiu M, Ho TV, Long DT, Walter JC, **Schärer OD** (2012) Construction of plasmids containing site-specific DNA interstrand crosslinks for biochemical and cell biological studies. **Methods Mol Biol** 920, 203-219.
8. Yeo J-E, Khoo A, Fagbemi AF, **Schärer OD** (2012) The efficiencies of damage recognition and excision correlate with duplex destabilization induced by acetylaminofluorene adducts in human nucleotide excision repair. **Chem Res Tox**, 25, 2462-2468. PMCID: PMC3502718.
9. Hentschel S, Alzeer J, Angelov T, **Schärer OD**, Luedtke NW (2012) Synthesis of DNA interstrand crosslinks using a photocaged nucleobase. **Angew Chem**, 51, 3466-3469. Policy Exempt - Not resulting from NIH funding.
10. Fu YV, Yardimci H, Long DT, Ho TV, Guainazzi A, Bermudez VP, Hurwitz J, van Oijen A, **Schärer OD**, Walter JC (2011) Selective bypass of a lagging strand roadblock by the eukaryotic replicative DNA helicase. **Cell** 146, 931-941. PMCID: PMC3209622.
11. Ho TV, Guainazzi A, Derkunt SB, Enoiu M, **Schärer OD** (2011) Structure-dependent translesion synthesis of major groove DNA interstrand crosslinks. **Nucl Acids Res** 39, 7455-7464. PMCID: PMC3177197.

12. Guainazzi A, Campbell AJ, Angelov T, Simmerling C, **Schärer OD** (2010) Synthesis and molecular modeling of a nitrogen mustard DNA interstrand crosslink. **Chem Eur J** 16, 12100-12103.
13. Orelli B, McClendon BT, Tsodikov, OV, Ellenberger T, Niedernhofer LJ, **Schärer OD** (2010) The interaction between ERCC1 and XPA is required for nucleotide excision repair, but not other DNA repair pathways. **J Biol Chem** 285, 3705-3712.
14. Ahmad A, Enzlin JH, Wijgers N, Raams A, Appeldoorn E, Theil AE, Hoeijmakers JHJ, Vermeulen V, Jaspers NGJ, **Schärer OD\***, Niedernhofer LJ\* (2010) Aberrant sub-cellular localization of DNA repair protein XPF: the molecular basis for extracutaneous symptoms in xeroderma pigmentosum. **PLoS Genet** 6, e1000871. PMID:PMC2832669. \*Co-corresponding authors
15. Knipscheer P, Räsche M, Smorgorzewska A, Enoiu M, Ho TV, **Schärer OD**, Elledge SJ, Walter JC (2009) The Fanconi anemia pathway promotes replication-dependent DNA interstrand crosslink repair. **Science** 326, 1698-701. PMID: PMC2909596.

## D. RESEARCH SUPPORT

### Ongoing Research Support

R01CA165911-01 Schärer, OD (PI) 07/01/12-04/30/17

NIH/NCI

Synthesis, structure and repair of DNA interstrand crosslinks.

Role: PI

The major goals of this project are to synthesize and structurally characterize DNA interstrand crosslinks and to characterize how they are processed in cell extracts and by DNA polymerases.

3P01CA092584-11 Tainer, JA (PI) 09/01/11-08/31/16

NIH/NCI

Structural Cell Biology of DNA Repair Machines

Role: Senior Investigator

Structural and biochemical approaches to study the interaction of ERCC1-XPF with XPA, SLX4 and DNA

NN Begley TJ; Schärer, OD (Co-PIs) 11/01/13-10/31/15

SUNY/RF Research Collaboration Fund (PIs: Begley & Schärer)

Diagnostic Tools for Assessing the Levels and Repair of Cisplatin DNA Adducts in Tumors

Role: Co-PI

Generate antibodies with specificity against various cisplatin-DNA adducts

1R13 CA192553 Schärer, OD (PI) 11/07/14-03/13/15

NIH/NCI/NIA/NIEHS

2015 Mammalian DNA Repair Gordon Research Conference & Gordon Research Seminar

Role: PI

Support for the organization of a Gordon Research Conference and Seminar

### Recently Completed Research Support

P01ES04068 Grollman, A (PI) 07/01/07-08/31/12

NIH/NIEHS

Molecular Toxicology of DNA adducts

Role: Co-Investigator

R01GM080454-01 Schärer, OD (PI) 09/24/07-08/31/11

NIH/NIGMS

Coordination of late steps in the human nucleotide excision repair

R01GM080454-S1 Schärer, OD (PI) 08/14/09-06/31/11

NIH/NIGMS

Coordination of late steps in the human nucleotide excision repair

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Kollmar, Richard	POSITION TITLE Associate Professor, Cell Biology; Assistant Professor and Director of Basic Research, Otolaryngology		
eRA COMMONS USER NAME (credential, e.g., agency login) RKOLLMAR			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Julius-Maximilians-Universität Würzburg, Germany	(Vordiplom)	1983-1985	Chemistry
Ludwigs-Maximilians-Universität München, Germany	Dipl. Chem.	1985-1988	Chemistry
University of Wisconsin–Madison	Ph. D.	1988-1993	Cell and Molecular Biology
University of Texas Southwestern Medical Center	Postdoc	1993-1995	Neuroscience
Rockefeller University	Postdoc	1995-2003	Neuroscience

### A. Personal Statement

I am well suited to join Dr. Martello-Rooney in developing zebrafish into an affordable and high-throughput system to characterize pancreas other GI-derived biopsies from the underserved patient population. First, I have a broad scientific background in several disciplines—graduate training in cell and molecular biology obtained in the McArdle Laboratory for Cancer Research at the University of Wisconsin and postdoctoral training in neuroscience at Southwestern Medical Center and Rockefeller University. Second, I have more than two decades of experience working with zebrafish, starting out with the Neurobiology Course at the Marine Biological Laboratory in Woods Hole, establishing and leading a genetic screen as a postdoc, and continuing to study the molecular genetics of otolith formation in my own laboratory to the present day. We have identified several novel otolith proteins by using proteomics and are investigating their function both in vivo and in vitro. Third, I am leading a scientific collaboration with colleagues in Otolaryngology and in Physiology & Pharmacology to test novel treatments to promote regeneration of the recurrent laryngeal nerve after injury in the rat. This translational project extends a previous collaboration on Wnt signaling and the regeneration of spiral ganglion neurons. Both the otolith and the nerve-regeneration studies have been supported by external funding. Finally, with joint appointments in Cell Biology and Otolaryngology and as the Director of Basic Research for Otolaryngology, I have extensive experience in mentoring research by graduate and medical students, postdoctoral fellows, and residents.

### B. Positions and Honors

#### Positions and Employment

1988-1993	Research Assistant (with Peggy Farnham), McArdle Laboratory for Cancer Research, University of Wisconsin
1993-1995	Research Associate (with A. James Hudspeth), Howard Hughes Medical Institute and Department of Cell Biology and Neuroscience, University of Texas Southwestern Medical Center at Dallas
1995-2003	Research Associate (with A. James Hudspeth), Howard Hughes Medical Institute and Laboratory of Sensory Neuroscience, Rockefeller University, New York
2003-2009	Assistant Professor, Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign
2004-2009	Affiliate, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign
2009-2011	Visiting Associate Professor, Department of Cell Biology, SUNY Downstate Medical Center
2011-present	Assistant Professor, Department of Otolaryngology, SUNY Downstate Medical Center

2011-present Director of Basic and Translational Research, Department of Otolaryngology, SUNY Downstate Medical Center  
 2012-present Associate Professor, Department of Cell Biology, SUNY Downstate Medical Center  
 2013-present Director, Molecular and Cellular Biology Program, School of Graduate Studies, SUNY Downstate Medical Center

#### Other Experiences and Professional Memberships

1993 Neurobiology Course, Marine Biological Laboratory, Woods Hole, MA  
 2002-present Member, Association for Research in Otolaryngology  
 2003-present Member, Society for Neuroscience  
 2013-2015 NIH Special Emphasis Panel/Scientific Review Group on Xenopus Genetics and Genomics  
 2013-present Member, American Academy for Otolaryngology-Head and Neck Surgery

#### **C. Selected Peer-reviewed Publications (Out of 18 total)**

1. **Kollmar R**, Montgomery LG, Fak J, Henry LJ, Hudspeth AJ. Predominance of the  $\alpha 1D$  subunit in L-type voltage-gated  $Ca^{2+}$  channels of hair cells in the chicken's cochlea. *Proc Natl Acad Sci U S A*. 1997 Dec 23;94(26):14883-8. [PMC25132]
2. **Kollmar R**, Fak J, Montgomery LG, Hudspeth AJ. Hair cell-specific splicing of mRNA for the  $\alpha 1D$  subunit of voltage-gated  $Ca^{2+}$  channels in the chicken's cochlea. *Proc Natl Acad Sci U S A*. 1997 Dec 23;94(26):14889-93. [PMC25133]
3. **Kollmar R**. Who does the hair cell's 'do? Rho GTPases and hair-bundle morphogenesis. *Curr Opin Neurobiol*. 1999 Aug;9(4):394-8. Review. [PMID10448167]
4. **Kollmar R**, Nakamura SK, Kappler JA, Hudspeth AJ. Expression and phylogeny of claudins in vertebrate primordia. *Proc Natl Acad Sci U S A*. 2001 Aug 28;98(18):10196-201. [PMC56938]
5. Starr CJ, Kappler JA, Chan DK, **Kollmar R**, Hudspeth AJ. Mutation of the zebrafish choroideremia gene encoding Rab escort protein 1 devastates hair cells. *Proc Natl Acad Sci U S A*. 2004 Feb 24;101(8):2572-7. [PMC356991]
6. Kappler JA, Starr CJ, Chan DK, **Kollmar R**, Hudspeth AJ. A nonsense mutation in the gene encoding a zebrafish myosin VI isoform causes defects in hair-cell mechanotransduction. *Proc Natl Acad Sci U S A*. 2004 Aug 31;101(35):13056-61. [PMC516516]
7. López-Schier H, Starr CJ, Kappler JA, **Kollmar R**, Hudspeth AJ. Directional cell migration establishes the axes of planar polarity in the posterior lateral-line organ of the zebrafish. *Dev Cell*. 2004 Sep;7(3):401-12. [PMID15363414]
8. Asai Y, Chan DK, Starr CJ, Kappler JA, **Kollmar R**, Hudspeth AJ. Mutation of the zebrafish atrophin2 gene disrupts signaling by fibroblast growth factor during development of the inner ear. *Proc Natl Acad Sci U S A*. 2006 Jun 13;103(24):9069-74. [PMC1474007]
9. Vieira M, Christensen BL, Wheeler BC, Feng AS, **Kollmar R**. Survival and stimulation of neurite outgrowth in a serum-free culture of spiral ganglion neurons from adult mice. *Hearing Res*. 230: 17-23, 2007. [PMID17521837; manuscript available at <http://hdl.handle.net/2142/1353>]
10. Kang YJ, Stevenson A, Yau P, **Kollmar R**. Sparc Protein Is Required for Normal Growth and Mineralization of Zebrafish Otoliths. *JARO—Journal of the Association for Research in Otolaryngology* 9: 436-451, 2008. [PMC2580808]
11. Shah SM, Kang YJ, Christensen BL, Feng AS, **Kollmar R**. Expression of Wnt receptors in adult spiral ganglion neurons: Frizzled 9 localization at growth cones of regenerating neurites. *Neuroscience* 164: 478-487, 2009. [PMC2761969; manuscript also available at <http://hdl.handle.net/2142/14823>]
12. Shah SM, Patel CH, Feng AS, **Kollmar R**. Lithium alters the morphology of neurites regenerating from cultured adult spiral ganglion neurons. *Hear Res*. 304: 137-44, 2013. [PMC3773701]
13. Mor N, Naggar I, Das O, Nakase K, Silverman JB, Sundaram K, Stewart M, **Kollmar R**. Quantitative video laryngoscopy to monitor recovery from recurrent-laryngeal-nerve injury in the rat. *Otolaryngol Head Neck Surg*. in press.

#### **D. Research Support**

##### Ongoing Research Support

1 R21 DC013629-01A1 (NIH/NIDCD) Kollmar (PI) 12/1/14-11/30/16  
Restoration of Recurrent-Laryngeal-Nerve Function after Injury in a Rat Model  
This study aims to develop procedures for a reducible injury to the recurrent laryngeal nerve and to test the effect of systemic lithium administration on recovery from unilateral vocal-fold paralysis in rats.  
Role: Principal Investigator

Completed Research Support

2013 AAO-HNSF Percy Memorial Research Award Kollmar (PI) 7/1/13-6/30/14  
Restoration of recurrent-laryngeal-nerve function after injury in a rat model  
This study aims to develop surgical and pharmacological methods to promote nerve regeneration in rats with unilateral vocal-fold paralysis.  
Role: Principal Investigator

1 R01 DC006962-01A1 (NIH/NIDCD) Kollmar (PI) 7/1/05-6/30/13  
Molecular Genetics of Otolith Formation in the Zebrafish  
This study aims to identify the constituent proteins of otoliths and elucidate their role in otolith formation.  
Role: Principal Investigator

National Organization for Hearing Research Kollmar (PI) 2/1/2008-1/31/2009  
Interaction of Wnt-Frizzled- and BDNF-signaling during neurite regeneration from adult spiral ganglion neurons  
The long-term goal of this translationally-oriented project is to improve the fidelity of sound perception with cochlear implants by stimulating the outgrowth of neurites from damaged spiral ganglion neurons.  
Role: Principal Investigator

## BIOGRAPHICAL SKETCH

NAME Shroyer, Kenneth Reed	POSITION TITLE Marvin Kuschner Professor and Chairman Department of Pathology Stony Brook Medicine		
eRA COMMONS USER NAME SHROYER.KEN			
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Colorado College, Colorado Springs, CO	B.A.	1978	Biology
Univ. of CO Graduate School, Denver, CO	Ph.D.	1983	Experimental Pathology
Univ. of CO School of Medicine, Denver, CO	M.D.	1987	Medicine

### A. Personal Statement

Dr. Shroyer is Board Certified in Anatomic and Clinical Pathology (1991), with subspecialty certification in Cytopathology (1995). He is an experienced surgical pathologist and cytopathologist and has also maintained continuous federally-funded grant support since 1993. He was a member of the graduate school at the University of Colorado Health Sciences Center for more than 15 years and has been a member of the Molecular Biology Program at Stony Brook University since 2007. He has trained more than 40 graduate students, medical students, MSTP students, residents, and clinical fellows, many of whom have gone on to complete postdoctoral research fellowships, including some that now hold faculty positions in the United States, Europe and Japan. Dr. Shroyer's research has focused on the molecular characterization of benign, premalignant, and malignant lesions of the female genital tract and a wide range of other anatomic sites. He invented the method of DNP labeling of nucleic acid probes, was a pioneer in the development of methods for *in situ* hybridization of mRNAs in the early 1980s, and was the first to report the analysis of x-chromosome inactivation in archival tissues as a marker of clonality. His laboratory has developed and evaluated the expression of numerous novel molecular assays of cellular immortalization and malignant transformation, including telomerase, HPV, surviving, p16, and B7-H4, using PCR-based methods, immunohistochemistry, and *in situ* hybridization.

### B. Positions and Honors

#### Positions and Employment:

1987-1988	Intern in Anatomic and Clinical Pathology, University of Colorado Health Sciences Center
1988-1991	Resident in Anatomic and Clinical Pathology, Univ. of Colorado Health Sciences Center
1991	Chief Resident in Pathology, University of Colorado Health Sciences Center
1991-1997	Assistant Professor of Pathology, University of Colorado Health Sciences Center
1997-2001	Associate Professor with tenure, University of Colorado Health Sciences Center
2002-2007	Professor with tenure, University of Colorado Health Sciences Center
1991-2007	Graduate Faculty, University of Colorado Health Sciences Center, Graduate School
1993-2007	Director of Cytopathology, University of Colorado Health Sciences Center
2000-2007	Director of Surgical Pathology, University of Colorado Health Sciences Center
2007-present	Marvin Kuschner Professor and Chair, Department of Pathology, Stony Brook University Medical Center, State University of New York
1991-present	Graduate Faculty, Stony Brook University Medical Center, Molecular and Cellular Biology Program

### **Other Experience and Professional Memberships (selected):**

- 2004- Editorial Board, Human Pathology
- 2006- Associate Editor, Journal of Clinical Virology
- 2001- National Cancer Institute Study Section member, including IMAT, Applied Emerging Technologies for Cancer Research, Alliance of Glycobiologists for Detection of Cancer and Cancer Risk, SPOREs in Breast, Cervical, Endometrial, Ovarian, Skin Cancers, Lymphoma, Genitourinary, and Gastrointestinal Cancers and In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- 1991- United States and Canadian Academy of Pathology (Member of the Scientific Advisory Board)
- 1991- American Association for Cancer Research
- 1993- American Society of Cytopathology
- 2002- American Society for Investigative Pathology

### **Honors (selected):**

- 1985-1987 Edgar and Marion Adler Scholar Award, UCHSC
- 1987 Joseph and Regina Glaser Student Research Award, UCHSC
- 1991 Robert H. Fennell, Jr., M.D. Award, Department of Pathology, UCHSC
- Lucien J. Rubinstein Award for the Best Paper on Neuro-oncology. Shared with B.K. Kleinschmidt-DeMasters and M.A. Bitter. The American Association of Neuropathologists

### **Invention (selected):**

Regulation of B7-H4 Expression by miR-34 and its Clinical Utility  
 Stony Brook University Research Foundation Reference Number: R-8128  
 Co-Inventor with Jingfang Ju  
 Disclosure Date: 9/11/2008

### **C. Contribution to Science**

Over the course of my career as a physician/scientist, my research has been focused on the identification and validation of objective molecular approaches to improve diagnostic accuracy in surgical pathology and cytopathology. The ultimate aim of this research has been to provide pathologists with objective molecular markers of cancer that can be integrated and interpreted in the context of tissue histopathology and cytopathology. My initial research focused on the development of methods to define tissue clonality and immortalization, based respectively on the development of methods to define patterns of X-chromosome inactivation in archival microdissected specimens and on the analysis of telomerase expression. These studies contributed to the recognition that epithelial premalignant lesions of the female genital tract are composed of immortalized populations of cells, with key characteristics that overlap with those of invasive carcinoma.

A second major aim has been to identify cancer biomarkers that could be used to improve diagnostic accuracy for premalignant and malignant clinical tissue specimens. My lab pioneered early studies of p16 as a cervical cancer biomarker and was the first to deploy p16 testing as a marker used in Pathology diagnostic laboratories to improve diagnostic accuracy. This work subsequently was expanded to include the analysis of p16, MCMs, and other molecular markers of cervical cancer that could be applied to cervical cytology specimens, with the underlying of improving diagnostic accuracy of the Pap test. Most recently, my lab utilized mass spectrometry of laser capture microdissected tissue specimens and identified keratin 17 (K17) as prognostic biomarker predict patient survival, independent of tumor grade and stage.

## **Research Papers (selected)**

1. Keratin 17 in premalignant and malignant squamous lesions of the cervix: proteomic discovery and immunohistochemical validation as a diagnostic and prognostic biomarker. Escobar-Hoyos LF, Yang J, Zhu J, Cavallo JA, Zhai H, Burke S, Koller A, Chen EI, **Shroyer KR**. Mod Pathol. 2014 Apr;27(4):621-30. Epub 2013 Sep 20. PMID: 24051697
2. Immunohistochemical localization of HE4 in benign, borderline, and malignant lesions of the ovary. Georgakopoulos P, Mehmood S, Akalin A, **Shroyer KR**. Int J Gynecol Pathol. 2012 Nov;31(6):517-23. PMID: 23018214
3. Immunocytochemical colocalization of P16(INK4a) and Ki-67 predicts CIN2/3 and AIS/adenocarcinoma. Singh M, Mockler D, Akalin A, Burke S, Shroyer A, **Shroyer KR**. Cancer Cytopathol. 2012 Feb 25;120(1):26-34. PMID: 22162342
4. B7-H4 overexpression in ovarian tumors. Tringler, B, Liu W, Corral L, Torkko KC, Enomoto T, Davison S. Lucia MS, Heinz DE, Papkoff J, **Shroyer, KR**. Gynecol Oncol. 2006 Jan;100(1):44-52. Epub 2005 Oct 26. PMID: 16256178

## **Complete List of Published Work in MyBibliography:**

<http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/47427615/>

## **D. Research Support**

### **Active**

Department of Veterans Affairs Merit Review (Zucker) 10/01/09-09/30/13, 0.6 months  
 Reversibility of Epithelial Mesenchymal Transition in Prostate Cancer.  
 Kenneth R. Shroyer, Co-I

Department of Defense. (Sitharaman) 2009-2011  
 Tumor-targeting single-wall carbon nanotubes for microwave-based imaging and hyperthermia treatment of breast cancer: A small animal study.  
 Kenneth R. Shroyer, Consultant

NIH 1R33CA140084. (Robinson, Shroyer: Subcontract PI) 04/01/11-03/31/15, 0.6 months  
 Specific Detection of Cervical Cancers Using Cytometry-Based Molecular Diagnostics.

Coulter Foundation. Pre-clinical Evaluation of Carbon (Balaji Sitharaman) 2011-2013  
 Nanostructure-Based High-Performance Contrast Agent for Magnetic Resonance Imaging.  
 Kenneth R. Shroyer, Co-I

### **Completed**

Carol M. Baldwin Breast Cancer Research Award (Sitharaman) 11/03/08-11/02/09 0.6 months  
 Multifunctional Carbon Nanostructure-Based Platforms for Breast Cancer Theragnostics.  
 Kenneth R. Shroyer, Co-I

TRO Program, Proteomics Developmental Projects Award (Shroyer) 2009-2010  
 Identifying Biomarkers for Pre-malignant and Invasive Cervical Cancer.  
 Kenneth R. Shroyer, PI

TRO Program, Carol M. Baldwin Breast Cancer Research Award (Nemesure) 2009-2010  
 Evaluation of a Newly Designed Device for Breast Cancer Screening.  
 Kenneth R. Shroyer, Co-I

NIH/NCI 4R33CA110519-02 (Shroyer) 07/01/05-04/30/10 1.80 months  
R33 phased innovation and application award p16 and HPV in low-grade cervical cytologic specimens.  
Kenneth R. Shroyer, PI

Carol M. Baldwin Breast Cancer Research Award (Sitharaman) 11/03/08-11/02/09  
(Targeted Research Opportunities)  
Multifunctional Carbon Nanostructure-Based Platforms for Breast Cancer Theragnostics.  
Kenneth R. Shroyer, Co-I

Proteomics Developmental Projects Award (Kew) 11/03/08-11/02/09, 0.6 months  
Kenneth R. Shroyer, Co-I

Targeted Research Opportunities, Proteomics Developmental Projects Award (Kew) 11/03/08-11/02/09  
Kenneth R. Shroyer, Co-I

RCA125370A (Robinson) 01/01/07-12/31/08  
Specific Biomarkers for Detection of Cervical Cancer Cells Using Flow Cytometry score.  
Kenneth R. Shroyer, Consultant

National Cancer Institute, R21 (Shroyer) 08/01/04-06/30/08  
Phased innovation and application award. p16 and HPV in low-grade cervical cytologic specimens.  
Kenneth R. Shroyer, PI

## RESEARCH &amp; RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator			
Prefix:	First Name*: Ellen	Middle Name	Last Name*: Li
Suffix:			
Position/Title*:	Chief		
Organization Name*:	The Research Foundation for SUNY, Stony Brook University		
Department:	Medicine		
Division:	Gastroenterology Hepatology		
Street1*:	101 Nicolls Road-Health Sciences Center		
Street2:	T-17 Room 060		
City*:	Stony Brook		
County:			
State*:	NY: New York		
Province:			
Country*:	USA: UNITED STATES		
Zip / Postal Code*:	117948173		
Phone Number*:	631-444-2119	Fax Number:	631-444-8886
		E-Mail*:	ellen.li@stonybrook.edu
Credential, e.g., agency login: ELLENLI1			
Project Role*: Other (Specify)		Other Project Role Category: Core Lead	
Degree Type:		Degree Year:	
Attach Biographical Sketch*:		File Name	
Attach Current & Pending Support:		LiBiosketchP20031515.pdf	

PROFILE - Senior/Key Person				
Prefix:	First Name*: Moro	Middle Name	Last Name*: Salifu	Suffix:
Position/Title*:	Director, Nephrology Fellowship Program			
Organization Name*:	The Research Foundation for SUNY, Downstate Medical Center			
Department:	Medicine			
Division:	Nephrology			
Street1*:	450 Clarkson Ave			
Street2:				
City*:	Brooklyn			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	112030000			
Phone Number*:	718-270-1584	Fax Number:	E-Mail*: moro.salifu@downstate.edu	
Credential, e.g., agency login: morosalifu				
Project Role*: Co-Investigator			Other Project Role Category:	
Degree Type: MD,MBA,MPH			Degree Year:	
			File Name	
Attach Biographical Sketch*:				
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Joel	Middle Name H.	Last Name*: Saltz	Suffix:
Position/Title*:	Professor and Chair			
Organization Name*:	Stony Brook University			
Department:	Biomedical Informatics			
Division:				
Street1*:	100 Nicolls Road			
Street2:				
City*:	Stony Brook			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117940000			
Phone Number*:	6316381420	Fax Number:	E-Mail*: joelhsaltz@stonybrookmedicine.edu	
Credential, e.g., agency login: JOELHSALTZ				
Project Role*: Co-Investigator			Other Project Role Category:	
Degree Type: MD,PHD,MA,BS			Degree Year:	
			File Name	
Attach Biographical Sketch*:			Joel_Saltz_Bio_LiP20.pdf	
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Yalini	Middle Name	Last Name*: Senathirajah	Suffix:
Position/Title*:				
Organization Name*:		SUNY Downstate		
Department:				
Division:				
Street1*:		COLUMBIA UNIVERSITY HEALTH SCIENCES		
Street2:		Columbia University Medical Center		
City*:		NEW YORK		
County:				
State*:		NY: New York		
Province:				
Country*:		USA: UNITED STATES		
Zip / Postal Code*:		100323702		
Phone Number*:		Fax Number:		E-Mail*: ys334@columbia.edu
718-270-7770				
Credential, e.g., agency login: YSENATH				
Project Role*: Co-Investigator			Other Project Role Category:	
Degree Type: PHD,MS,AB			Degree Year:	
Attach Biographical Sketch*:			File Name	
Attach Current & Pending Support:			biosketch_P20grant_Senathirajah.pdf	

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2015

End Date\*: 08-31-2016

Budget Period: 1

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Ellen		LI		PD/PI	183,300.00	3.0			45,825.00	26,074.00	71,899.00
2.	Joel		Saltz		Co-I	183,300.00	0.3			4,583.00	2,608.00	7,191.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	79,090.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							79,090.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

1,322.00

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>1,322.00</b>
--------------------------	-----------------

**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	4,116.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
<b>Total Other Direct Costs</b>	<b>4,116.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>84,528.00</b>

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1. MTDC	58.0	80,362.00	46,610.00
2. DownState	61.5	4,116.00	2,531.00
Total Indirect Costs			49,141.00
Cognizant Federal Agency	DHHS 2/21/2014 Louis Martollotti		
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>133,669.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: SBU_P20_Administrative_Core_Budget_Justification.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 2

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2016

End Date\*: 08-31-2017

Budget Period: 2

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Ellen		LI		PD/PI	183,300.00	3.0			45,825.00	26,074.00	71,899.00
2.	Joel		Saltz		Co-I	183,300.00	0.3			4,583.00	2,608.00	7,191.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	79,090.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							79,090.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

1,174.00

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>1,174.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	4,155.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
<b>Total Other Direct Costs</b>	<b>4,155.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>84,419.00</b>

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1. MTDC	58.0	80,264.00	46,553.00
2. DownState	61.5	4,155.00	2,555.00
Total Indirect Costs			49,108.00
Cognizant Federal Agency	DHHS 2/21/2014 Louis Martollotti		
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>133,527.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: SBU_P20_Administrative_Core_Budget_Justification.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2017      End Date\*: 08-31-2018      Budget Period: 3

A. Senior/Key Person													
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*	
1.	Ellen		LI		PD/PI	183,300.00	3.0			45,825.00	26,074.00	71,899.00	
2.	Joel		Saltz		Co-I	183,300.00	0.3			4,583.00	2,608.00	7,191.00	
Total Funds Requested for all Senior Key Persons in the attached file													
Additional Senior Key Persons:			File Name:								Total Senior/Key Person		79,090.00

B. Other Personnel							
Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
						Total Salary, Wages and Fringe Benefits (A+B)	79,090.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

1,102.00

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>1,102.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	4,187.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
<b>Total Other Direct Costs</b>	<b>4,187.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>84,379.00</b>

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1. MTDC	58.0	80,192.00	46,511.00
2. DownState	61.5	4,187.00	2,575.00
Total Indirect Costs			49,086.00
Cognizant Federal Agency	DHHS 2/21/2014 Louis Martollotti		
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>133,465.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: SBU_P20_Administrative_Core_Budget_Justification.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 4

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2018

End Date\*: 08-31-2019

Budget Period: 4

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Ellen		LI		PD/PI	183,300.00	3.0			45,825.00	26,074.00	71,899.00
2.	Joel		Saltz		Co-I	183,300.00	0.3			4,583.00	2,608.00	7,191.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	79,090.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							79,090.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

1,078.00

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>1,078.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	4,187.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
<b>Total Other Direct Costs</b>	<b>4,187.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>84,355.00</b>

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1. MTDC	58.0	80,168.00	46,497.00
2. DownState	61.5	4,187.00	2,575.00
Total Indirect Costs			49,072.00
Cognizant Federal Agency	DHHS 2/21/2014 Louis Martollotti		
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>133,427.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: SBU_P20_Administrative_Core_Budget_Justification.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## **Budget Justification – Administrative Core (Institutional)**

### **A. Key Personnel:**

1. Ellen Li, M.D.-Ph.D. Contact PI. Dr. Li will devote 3 calendar months to this project at the NIH cap salary and fringes. Dr. Li is Professor of Medicine and Microbiology and Molecular Genetics, and Chief of the Division of Gastroenterology and Hepatology at Stony Brook Medicine. She will oversee integration of the SUNY Stony Brook and Downstate GI Biobanks and will oversee the planning of an integrated biomedical informatics platform that will link the samples and metadata collected within the GI Biobanks with downstream data.
2. Joel Saltz, M.D.-Ph.D. Dr. Saltz will devote 0.3 calendar months to this project at the NIH cap salary and fringes. Dr. Saltz is the Cherith Professor and Founding Chair of the Biomedical Informatics Department at Stony Brook University, Associate Director of Stony Brook University Cancer Center and fellow of the American College of Medical Informatics. He also holds a secondary appointment in the Department of Pathology. Dr. Saltz will coordinate with Dr. Yalini Senathirajah on planning the development of an integrated biomedical informatics platform.

**B. Other Personnel:** none

**C. Equipment:** none.

**D. Supplies:** none

**E. Travel:** Requested to partially reimburse a Key Personnel to attend a biennial PACHE workshop or a national meeting.

### **F. Other Expenses:**

Subcontract: \$ 4,102 is requested for Administrative Core Key Personnel at SUNY Downstate Medical Center (Dr. Yalini Senathirajah, Assistant Professor of Bioinformatics who will coordinate planning the development of an integrated biomedical informatics platform.)

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	Totals (\$)	
Section A, Senior/Key Person		316,360.00
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		316,360.00
Section C, Equipment		0.00
Section D, Travel		4,676.00
1. Domestic	4,676.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		16,645.00
1. Materials and Supplies	0.00	
2. Publication Costs	0.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	16,645.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	0.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		337,681.00
Section H, Indirect Costs		196,407.00
Section I, Total Direct and Indirect Costs (G + H)		534,088.00
Section J, Fee		0.00

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2015

End Date\*: 08-31-2016

Budget Period: 1

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Moro		Salifu		PD/PI		0.5			0.00	0.00	0.00
2.	Yalini		Senathirajah		Co-I	104,526.00	0.3			2,618.00	1,498.00	4,116.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	4,116.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							4,116.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
<b>Total Other Direct Costs</b>	<b>0.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>4,116.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. MTDC	61.5	4,116.00	2,531.00
<b>Total Indirect Costs</b>			<b>2,531.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>6,647.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: P20_grant-Budget_justification_Admin_Core_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 2

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2016

End Date\*: 08-31-2017

Budget Period: 2

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Moro		Salifu		PD/PI		0.5			0.00	0.00	0.00
2.	Yalini		Senathirajah		Co-I	104,526.00	0.3			2,618.00	1,537.00	4,155.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	4,155.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							4,155.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
<b>Total Other Direct Costs</b>	<b>0.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>4,155.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. MTDC	61.5	4,155.00	2,555.00
<b>Total Indirect Costs</b>			<b>2,555.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>6,710.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
---------------	------------------------------

<b>K. Budget Justification*</b>	File Name: P20_grant- Budget_justification_Admin_Core_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 3

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 3

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Moro		Salifu		PD/PI		0.5			0.00	0.00	0.00
2.	Yalini		Senathirajah		Co-I	104,526.00	0.3			2,618.00	1,569.00	4,187.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons:		File Name:		Total Senior/Key Person								4,187.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							4,187.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>0.00</b>
--------------------------	-------------

**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
<b>Total Other Direct Costs</b>	<b>0.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>4,187.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. MTDC	61.5	4,187.00	2,575.00
<b>Total Indirect Costs</b>			<b>2,575.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>6,762.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: P20_grant-Budget_justification_Admin_Core_2015.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 4

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2018End Date\*: 08-31-2019Budget Period: 4

A. Senior/Key Person													
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*	
1.	Moro		Salifu		PD/PI		0.5			0.00	0.00	0.00	
2.	Yalini		Senathirajah		Co-I	104,526.00	0.3			2,618.00	1,569.00	4,187.00	
Total Funds Requested for all Senior Key Persons in the attached file													
Additional Senior Key Persons:			File Name:								Total Senior/Key Person		4,187.00

B. Other Personnel							
Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							4,187.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>0.00</b>
--------------------------	-------------

**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
<b>Total Other Direct Costs</b>	<b>0.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>4,187.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. MTDC	61.5	4,187.00	2,575.00
<b>Total Indirect Costs</b>			<b>2,575.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>6,762.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: P20_grant-Budget_justification_Admin_Core_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## **Feasibility Studies to Build Collaborative Partnerships in Cancer Research (P20)**

### **Feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research**

#### **BUDGET JUSTIFICATION – Administrative Core**

##### **PERSONNEL**

Moro Salifu, MD, MBA, MPH: Principal Investigator (0.6 calendar months, 5% effort (in-kind), Years 1-4)

Dr. Salifu, Professor of Medicine, is the Chair of the Department of Medicine and Chief of the Division of Nephrology. Dr. Salifu also is the Director of the Brooklyn Health Disparities Center (BHDC) and Principal Investigator of the P20 grant supporting the expansion of activities of the BHDC. Dr. Salifu will be involved with the Administrative Core of the overall project.

Yalini Senathirajah, PhD: Co-Investigator (0.3 calendar months, 2.5% effort, Years 1-4)

Dr. Senathirajah, Assistant Professor, is in the Department of Medical Informatics within the College of Health Related Professions. Dr. Senathirajah will be involved with the clinical data integration to create a shared resource that can be utilized for downstream research analysis in collaboration with Dr. Joel Saltz at Stony Brook.

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	Totals (\$)	
Section A, Senior/Key Person		16,645.00
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		16,645.00
Section C, Equipment		0.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		0.00
1. Materials and Supplies	0.00	
2. Publication Costs	0.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	0.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		16,645.00
Section H, Indirect Costs		10,236.00
Section I, Total Direct and Indirect Costs (G + H)		26,881.00
Section J, Fee		0.00

## PHS 398 Cover Page Supplement

OMB Number: 0925-0001

## 1. Project Director / Principal Investigator (PD/PI)

Prefix:

First Name\*: Ellen

Middle Name:

Last Name\*: Li

Suffix:

## 2. Human Subjects

Clinical Trial? ☒ No ☐ YesAgency-Defined Phase III Clinical Trial?\* ☐ No ☐ Yes

## 3. Permission Statement\*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes ☐ No

## 4. Program Income\*

Is program income anticipated during the periods for which the grant support is requested? ☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount (\$)*	Source(s)*
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

## PHS 398 Cover Page Supplement

### 5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?\*      ☒ No      ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: [http://grants.nih.gov/stem\\_cells/registry/current.htm](http://grants.nih.gov/stem_cells/registry/current.htm). Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s):      ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

### 6. Inventions and Patents (For renewal applications only)

Inventions and Patents\*:      ☐ Yes      ☒ No

If the answer is "Yes" then please answer the following:

Previously Reported\*:      ☐ Yes      ☐ No

### 7. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name\*:

Middle Name:

Last Name\*:

Suffix:

☐ Change of Grantee Institution

Name of former institution\*:

## PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	IntroductionAdminCoreCSHL_FINAL.pdf
2. Specific Aims	AdminCoreSpecificAimsCSHL_FINAL.pdf
3. Research Strategy*	AdminCoreResStrategyCSHL_FINAL.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	
6. Inclusion of Women and Minorities	
7. Inclusion of Children	
Other Research Plan Sections	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	Admin_LOS.pdf
13. Resource Sharing Plan(s)	
Appendix (if applicable)	
14. Appendix	

## 1. INTRODUCTION – ADMINISTRATIVE CORE

In this revised planning grant submission entitled “Partnership to Study Racial/Ethnic Differences in GI Cancer Biology” in response to PAR-14-152, we have made many changes in response to the reviewers’ thoughtful comments. We were pleased that the reviewers felt that the Administrative Core “...fulfills all the expected requirements for managing the interactions among the three partnering institutions” and that “...the principal investigators/core directors have significant administrative skills...” The reviewers however commented that “...The approaches used are standard and there are no truly innovative aspects of data sharing and/or trainee monitoring... Possible pitfalls and alternative approaches in priority-setting, implementation, and evaluation are not adequately described...-There is no External Advisory Board to monitor progress.”

In the revised **Administrative Core**, we have put greater emphasis on planning the development of an integrative bioinformatics platform that will facilitate not only data sharing between the three institutions but also with the larger research community. **Dr. Joel Saltz** has replaced Dr. Scott Powers, who will no longer be able to devote the effort required. **Dr. Joel Saltz** is founding Chair of the Department of Biomedical Informatics at SUNY Stony Brook and Associate Director of the Stony Brook Cancer Center. We have also added **Dr. Yalini** to the Administrative Core. Drs. **Saltz** and **Senathirajah** will assist in planning a platform that will link coded samples with longitudinal clinical metadata and downstream molecular and histologic data generated from the two SUNY campuses. We hope that these changes will address concerns raised by the reviewers that “there are no truly innovative aspects of data sharing.”

In the revised **Administrative Core**, we have modified the composition of the Internal Advisory Committee as suggested by the reviewers. The Internal Advisory Board will now be co-chaired by **Dr. Patricia Thompson**, who was recently recruited to the Stony Brook Cancer Center as Associate Director of Basic Research and by **Dr. Alea Mills**, Professor at CSHL. **Dr. Patricia Thompson** leads a nationally prominent research program that has focused on the evolution of molecular and cellular changes that occur during the development of colorectal and breast cancer. Her research is concentrated primarily on the discovery and validation of biomarkers that help identify individuals at greatest risk for cancer recurrence, to enable more precise and effective methods to treat cancer patients. **Dr. Alea Mills** is an accomplished scientist, who has used chromosome engineering to identify critical tumor suppressor genes involved in cancer. **Dr. Michael Wigler**, Professor at CSHL will join this committee as a representative of CSHL. He is a very distinguished scientist who has been at the forefront in developing single-cell DNA and RNA analysis of cancer cells. They will be charged with overseeing priority setting, implementation and evaluation of the P20 progress.

As suggested by the reviewers, we have added a three member External Advisory Board, which will be chaired by Dr. John Carethers, Chairman of Medicine at the University of Michigan, and a leading expert on mismatch repair in colon cancer biology and on African American differences in colon cancer biology. The External Advisory Board will provide an additional independent layer of oversight of priority setting, implementation and evaluation of the pilot research projects in the Cancer Research Program and of the Training and Education Program. We have expanded our discussion on shifting priorities in pilot research projects based on review of progress and success of these projects in generating publications and larger research awards to pursue the objectives originally outlined in the pilot projects.

We have also substantially revised our plans in the Training and Education Program. We now propose to develop a tri-institutional Scholars in BioMedical Sciences in Cancer Health Disparities that operates on the concepts introduced by the HHMI “med into grad” programs to enhance the training of graduate students in translational medicine. This program will be built on an existing Scholars in BioMedical Scholars Program that was initiated two years ago at SUNY Stony Brook. We anticipate that developing this program will boost recruitment of talented URM students to the graduate programs of all three institutions. We have expanded our discussion of the metrics by which we will evaluate the program by continued longitudinal tracking of the trainees after they leave the program, and by monitoring the number of URM students matriculating from the graduate programs at all three institutions.

## ADMINISTRATIVE CORE – SPECIFIC AIMS

Individually, each of the participating institutions have significant and complementary strengths that can be applied towards filling the knowledge gap for racial/ethnic differences in GI cancer biology. For example, SUNY Stony Brook has exceptional strengths in computational sciences and in the molecular and cellular biology of cancer. SUNY Downstate has a demonstrated track record of URM graduate and medical education and scientific excellence in health disparities research and education. Furthermore the demographics of their patient population (75% African American) make development of a SUNY Downstate GI Biobank a very high priority. Finally the NCI-designated Cancer Center at CSHL provides world-renown shared resources and ‘omics’ technologies. The overarching goal of the Institution’s (SUNY) and Cancer Center Administrative Cores is to integrate, and coordinate the activities of SUNY Stony Brook, SUNY Downstate and CSHL, such that “the parts add up to more than the whole.” For this reason the Administrative Cores will be combined into a single Steering Committee to implement the following Specific Aims:

**Specific Aim 1. Build an integrative partnership between two SUNY medical campuses, Stony Brook and Downstate, and the NCI-designated Cancer Center at Cold Spring Harbor Laboratory to study racial and ethnic differences in GI cancer biology using state of the art technologies.** The Steering Committee will plan on building the Downstate GI Biobank and integrating it with the existing Stony Brook GI Biobank. While the collection effort for colorectal cancer and pancreatic cancer tissue specimens are directed primarily for pilot projects **P1** and **P2**, we anticipate that the number of specimens collected will exceed the number that are analyzed in the pilot projects **P1** and **P2**. These additional specimens will be archived for analysis when we have accumulated sufficient preliminary data to submit applications for larger research awards, or distributed to other investigators. Furthermore, in anticipation of future studies, we plan to collect parallel blood and stool samples, which will be reserved for future studies conducted by the current or outside investigators.

The value of the samples relate to how well we link the information linked to these samples. This information includes both longitudinal clinical metadata with defined clinical endpoints and the molecular and histological data generated from the samples. Because access to care may also affect clinical outcome, it is very important that data measuring this access (e.g. health insurance data) is also collected as important potentially confounding variables. For this reason we have enlisted biomedical informaticians at both SUNY Stony Brook and Downstate to assist in planning the development of an integrative biomedical informatics platform. To begin with the Steering Committee will work to develop a common list of data elements with a common controlled vocabulary in order to facilitate transfer of information between institutions. Both the Internal Advisory Committee and the External Advisory Board will serve to monitor progress made by the Steering Committee in implementing this aim. They will also serve to monitor progress of the two pilot projects and advise whether the projects need to be modified or replaced over the four years of this award.

**Specific Aim 2. Build an integrative partnership to promote recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies.** To enhance the research capacities, knowledge and diversity among our cancer research faculty and fellows with research interest in cancer health disparities, we propose to develop a ‘Scholars in Biomedical Sciences for Cancer Health Disparities’ program for graduate students, particularly those from underrepresented and underserved communities that emphasizes the bench to community cancer care delivery continuum. We will also sponsor an annual Cancer Health Disparities symposium aimed at developing cross-cultural competency in the research workspace including mentorship toward hypothesis based cancer research, and to build awareness of cancer health disparities research findings. The Steering Committee, with oversight from the Internal Advisory Committee and the External Advisory Board, will track trainee progression to independence and R01 funding and scientific quality, retention in research, professional work satisfaction and exceptional performance in the research workspace ---the true measures of success.

## **ADMINISTRATIVE CORE – RESEARCH STRATEGY**

### **1. Significance.**

It is well established that both the incidence and mortality of colorectal cancer and pancreatic cancer are significantly higher in African Americans than in any other racial/ethnic group [1-8]. Emerging technologies in genomics and bioinformatics have been applied in national networks such as the Cancer Genome Atlas Network to accelerate the molecular understanding of the genetic basis of cancers. However the representation of data from URM subjects such as African Americans (AA) is very low. The published TCGA colorectal cancer data includes only 6 subjects that are identified as African American [9]. This highlights a critical need for generating more data from underrepresented minority (URM) subjects, particularly those of African descent.

We also recognize there are substantial barriers to racial/ethnic minority applications for extramural funding [10]. Part of that barrier relates to barriers in accessing URM clinical biospecimens.

Precision medicine is now emerging as clinical practice in top U.S. cancer hospitals. With unclear costs, the inevitable lag to community practice, and a gross lack of population diversity in ongoing genomics research, a further widening of disparity in cancer care seems inevitable. The ability to generalize advances in cancer omics to all patients depends on an understanding of how underlying population differences affect tumor biology, cancer behavior in the clinic and patient factors. Thus, the full impact of the 'precision oncology' promise will only be achieved when advances in care are effectively translated from academic centers to community practice. The integration of faculty, fellows and students from underrepresented and medically underserved communities in the research workforce with efforts to enhance awareness of health disparities in the established research workforce is needed to identify, study and solve issues of cancer health disparities.

We are proposing a partnership between two major SUNY universities (Institutional) and the NCI designated Cancer Center at Cold Spring Harbor Laboratory (Cancer Center), to study racial/ethnic differences in GI cancer biology that builds upon complementary strengths. The two SUNY universities, Stony Brook University and Downstate Medical Center, serve both to educate and to provide health care for URM communities. SUNY Downstate Medical Center together with the SUNY Stony Brook University is one of the 62 research universities that comprise the Association of American Universities (AAU) and is ranked among the top thirty-five public research universities in the US and among the top 1% universities in the world. It is a top-tier university that educates large numbers of students from low-income families and from diverse backgrounds, especially in high need areas such as science, technology, engineering and mathematics (STEM). Stony Brook University has a substantial minority enrollment and was included in the 2013 Education Trust Report of higher education institutions that are leading in closing the minority college-completion gap. SUNY Downstate Medical Center does not have an undergraduate campus, but is the SUNY-system leader in training minority healthcare professionals, ranking fourth nationally - only behind the 3 Historically Black Medical Colleges - in the number of minority faculty on staff, and has a student body that is 55% minority. SUNY Downstate Medical Center is first among all schools in New York State in the number of URM students. The NCI-designated Cancer Center at Cold Spring Harbor Laboratory (CSHL) has been at the forefront of research into the molecular biology of cancer and at developing new technologies, but does not have a medical facility and consequently does not have direct access to cancer patients. CSHL investigators are eager to directly address the question of racial and ethnic disparities in GI cancers through this partnership.

### **2. Innovation.**

One of the key innovations in this proposal is to plan the development of an integrative biomedical informatics platform that will link patient samples (GI tissues, blood, stool) with rigorously curated longitudinal clinical metadata with defined clinical endpoints on the one hand, as well as molecular and histological data generated from the patient samples (from multiple investigators). The key concept is that generating a repository of linked data is the ultimate goal of creating the BioBanks, and maintaining the linkage between datasets begins with the collection and distribution of the patient samples by the proposed SUNY GI Biobanks, which are controlled in a modular fashion by the respective Institutions. The rationale for the proposed organization of the SUNY Stony Brook GI Biobank is based on previous litigation about ownership of patient samples (Washington University vs. William J. Catalona) and the requirement in the state of New York that SUNY Biobanks have a state biobanking license. On the other hand the clinical metadata collected on the patient and the research data generated from the patient samples are the intellectual property of the investigator that generated the data. Because investigators will often be required to share their data with

other investigators, particularly if the research is supported by federal funds, we plan to generate an integrative biomedical informatics platform that will facilitate data sharing.

While the collection process of both samples and clinical metadata will be under the control of the individual SUNY universities, Stony Brook and Downstate, it is critical for these collaborative studies that the data and samples be collected in an identical manner using the same standard operating procedures and using the same data elements and controlled vocabulary. The collection process and proposed linkage of data in the SUNY GI Biobanks is summarized in **Table 1**.

**Table 1. Linkage of clinical data, patient samples, downstream products and downstream data in integrated biomedical informatics platform.**

Clinical Data	Patient Samples	Downstream Products	Downstream Data
Encounter 1	Blood 1	Serum	
		Plasma	
		PMBC DNA, RNA	<b>Germline sequence</b>
	Stool 1	RNA later	
		Fresh Frozen	
	Tissue (tumor) 1	Fresh Tissue	<b>Organoids</b> , xenograft, cell lines
		Formalin Fixed	Histology, Immunohistochemistry, miRNA
		RNA later	<b>RNA-Seq, DNA Seq,</b>
		Fresh Frozen	RNA-Seq, DNA-Seq, Immunohistochemistry
	Tissue ("normal") 1	Fresh Tissue	Organoids, xenograft, cell lines
		Formalin Fixed	Histology, Immunohistochemistry, miRNA
		RNA later	<b>RNA-Seq, DNA-Seq,</b>
		Fresh Frozen	RNA-Seq, DNA-Seq, Immunohistochemistry

Individual encounters will be linked primarily to endoscopic procedures and to surgical operations where patient tissue samples will be collected. For pilot project **P1** Encounter 1 will generally be surgical resection of the colorectal cancer. Since 2010, the Stony Brook GI Biobank has been systematically collecting every surgical resection colorectal cancer specimen (as well as non cancer colorectal cancer specimens as controls), blood, and preoperative stool (total patients = 600). Encounter 2 will be the colonoscopic surveillance scheduled one year after the surgery.

For pilot project **P2**, Encounter 1 may be the diagnostic endoscopic ultrasound guided fine needle core biopsy (EUS-FNB) for patients referred to the GI interventional endoscopists at SUNY Stony Brook and SUNY Downstate for a tissue diagnosis of solid pancreatic mass. Surgical resection of the pancreatic mass may be Encounter 2 or if the EUS-FNB diagnosis was made elsewhere, Encounter 1. Further encounters may involve surgical resection of solitary colon cancer metastases or FNB of colon cancer and/or liver metastases. The patient samples will be stripped of identifying information and linked by a patient code, the encounter number, and sample ID.

Clinical data include established risk factors for colon cancer and pancreatic cancer and defined clinical outcomes (e.g. time to recurrence, time to metastases). Because we anticipate conducting future studies linking the gut microbiome to host factors, dietary information and stool is also being collected in all patients with colon cancer and pancreatic cancer. Because access to health care is a confounding factor, we have been collecting and recording information on patient's health insurance status (e.g. Private, Medicare, Medicaid, uninsured). The clinical data will be collected by clinicians and Biobank staff at the time of the encounter and reviewed with the patient's electronic medical record. All the data will be stripped of identifying information and linked to a patient code and encounter. Note that the samples proposed to be analyzed will be only a fraction of those that will be collected.

Another innovation is the engagement of **clinicians** at the outset in the design and execution of translational projects and in co-mentoring trainees involved in translational projects supported by the SUNY GI Biobanks. The organization of the collection effort is modeled along the clinical service line responsible for caring for GI cancer patients. In this way we can identify and obtain consent of potential subjects scheduled for surgery or endoscopic procedures for clinical care, and ensure that the GI Biobank staff are present to collect the surgical or endoscopic tissue biopsies, rapidly transport the fresh tissues (for organoids) and monitor QA (e.g. RIN scores of tissue RNA). For the Stony Brook Biobank, the initial clinical annotation of existing archived FFPE tissue specimens and the prospective collection of samples were driven by projects initiated by two Stony Brook URM junior clinical faculty members, Drs. **Denoya** and **Bucobo** [11,12]. Pilot

project **P1** arose from efforts of the SUNY Stony Brook GI Biobanks effort to support the research program of a URM SUNY Stony Brook research scientist, **Dr. Jennie Williams**. In addition, the Biobank has provided trainees at different career stages (undergraduates, medical students, residents and fellows) with experience and training in the collection and processing of biospecimens, the curation of clinical metadata, and integrated analysis to enable them to conduct clinical translational research in future steps of their careers. Thus the clinicians engaged in collecting the samples and consenting the patients are major stakeholders in the GI Biobanks and participate in the decision on the distribution of patient samples to various projects.

To facilitate the exchange of information and ideas and to evaluate new projects, SUNY Stony Brook has hosted a monthly GI Research Meeting that is video-streamed to SUNY Downstate and CSHL. At these meetings, work in progress for projects utilizing patient samples, such as **P1** and **P2**, have been presented and discussed among the participants at the three institutions. Furthermore, investigators requesting GI Biobank samples are asked to present their proposed project in the monthly GI Research Meeting to obtain feedback from both clinicians and other research investigators, prior to making decisions on allocation of patient samples.

### **3. Leadership**

**3A. History of Developing the P20 Leadership Team.** The composition of this leadership team is based on the history of the connections made between investigators at the three participating institutions. As part of an ongoing effort to mentor and support R01 funded URM investigator **Jennie Williams** and her interest in GI cancers and health disparities among AAs, as well as URM clinician, **Paula Denoya**, who was interested in colon cancer epigenetics, **Dr. Li**, the SUNY (Institutional) contact PI and **Dr. McCombie** the CSHL (NCI-Cancer Center) contact PI developed a collaboration to explore applying high resolution mapping of methylation using sequencing technology towards characterizing biological differences between AA and CA colon cancer tumors. However a major barrier to conducting this project was lack of access to URM specimens. Dr. Li made arrangements for RNA and DNA from existing URM specimens archived at the Washington University St. Louis Siteman Cancer Center to be sent to Dr. **Williams'** laboratory, but these samples lacked detailed clinical annotation with respect to potentially confounding covariates such as smoking, diabetes, obesity, etc. Consequently when **Dr. Li**, as one of three SUNY Health Network Presidential fellows, met **Dr. Mark Stewart**, Vice Dean of Research at SUNY Downstate, who was leading the effort to create a SUNY Health Network of Excellence, it was clear that a logical extension of the partnership would be to bring in SUNY Downstate, where the patient demographics include a minority majority (>70% African American). Dr. **Mark Stewart** subsequently arranged for Dr. **Li** to meet with Dr. **Moro Salifu**, Chair of Medicine and Director of the Brooklyn Health Disparity Center. Dr. **Salifu** in turn introduced Dr. **Li** to Dr. **Martello-Rooney** to begin developing an infrastructure at SUNY Downstate to collect and archive URM GI cancer specimens by focusing on pilot research projects P1 and P2. Dr. **Martello-Rooney's** own research program focuses on developing novel therapies of pancreatic cancers.

### **3B. Overview of Leadership to Implement Objectives of Overall Research Strategy (See Figure 1).**

To implement the objectives of our overall research strategy we plan to fuse the leadership of the SUNY (Institutional) Administrative Core and the leadership of CSHL (NCI-designated Cancer Center) Administrative Core into a central Steering Committee. The Steering Committee will meet monthly to review the progress of the two pilot research projects in the Cancer Research Program and the Training and Education Program. The Steering Committee will make joint decisions on reallocation of resources within the Cancer Research Program and the Training and Education Program as projects mature and additional extramural funding is secured. The Steering Committee will be advised by an Internal Advisory Committee composed of equal numbers of SUNY (Institutional) and CSHL Cancer Center representatives who will meet with the Steering Committee on a quarterly basis. The Steering Committee will be advised by an External Advisory Board, which is composed of leading experts in colon cancer, pancreatic cancer and community outreach. The External Advisory Board will meet annually with the Steering Committee and the Internal Advisory Committee in conjunction with the annual Symposium on Cancer Health Disparities hosted at the Brooklyn Health Disparities Center located on the SUNY Downstate campus. The two major objectives of our overall research strategy are:

1. Build an integrative platform for the three institutions to interact on all aspects of translational GI cancer research that would be present in a larger scale program, such as coordinating sample and data transfer, and to facilitate group communication and decision making and trouble-shooting.

2. Promote recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies. This will include building mentorship capacity among established cancer research investigators.

#### P20 EXTERNAL ADVISORY BOARD

John Carethers, MD	U. of Michigan
Antonio Baines, Ph.D.	NCCU
Marilyn Fraser-White, M.D.	Arthur Ashe Institute

#### P20 STEERING COMMITTEE

##### Institution (SUNY) Administrative Core

<u>Ellen Li, M.D.-Ph.D., PI</u>	Stony Brook
Joel Saltz M.D.-Ph.D. co-I	Stony Brook
Moro Salifu M.D. co-I	Downstate
Yalini co-I	Downstate

##### Cancer Center (CSHL) Administrative Core

<u>W. Richard McCombie, Ph.D. PI</u>
David Tuveson, M.D.,-Ph.D.co-I

#### P20 INTERNAL ADVISORY COMMITTEE

##### Institution (SUNY)

<u>Patricia Thompson Ph.D. co-chair</u>	Stony Brook
Mark Stewart M.D. -Ph.D.	Downstate

##### Cancer Center (CSHL)

<u>Alea A. Mills Ph.D co-chair</u>
Michael Wigler Ph.D

#### P20 CANCER RESEARCH PROGRAM

##### Institution (SUNY)

###### P1

<u>Jennie Williams, Ph.D. co-PI</u>	Stony Brook
Laura Martello-Rooney, Ph.D, co-I	Downstate
Paula Denoya, M.D, co-I.	Stony Brook

###### P2

<u>Gerardo Mackenzie, Ph.D. co-PI</u>	Stony Brook
Shivakumar Vignesh, M.D., co-I	Downstate
Juan Carlos Bucobo, co-I	Stony Brook
Laura Martello-Rooney, Ph.D, co-I	Downstate

##### Cancer Center (CSHL)

###### P1

<u>W. Richard McCombie, Ph.D.co-PI</u>
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###### P2

<u>David Tuveson, M.D,-Ph.D, co-PI</u>
----------------------------------------

#### P20 TRAINING AND EDUCATION PROGRAM

##### Institution (SUNY)

<u>Patricia Thompson Ph.D. co-PI</u>	Stony Brook
<u>Moro Salifu M.D. co-PI</u>	Downstate
Mark Stewart M.D-Ph.D.. co-I	Downstate

##### Cancer Center (CSHL)

<u>W. Richard McCombie, Ph.D. co-PI</u>
Alyson Kass-Eisler, Ph.D. Training Coord.

Fig. 1. Organizational Chart of P20 Scientific and Administrative Leadership.

### **3B1. Composition of the P20 Steering Committee**

#### P20 SUNY (Institutional) Administrative Core

**Ellen Li, M.D.-Ph.D.** (contact PI, SUNY Stony Brook) Dr. Ellen Li will oversee the integration of the SUNY GI Biobanks and the planning of an integrative biomedical informatics platform. She is Professor of Medicine and Chief of the Division of Gastroenterology and Hepatology at Stony Brook University. She is also Professor of Molecular Genetics and Microbiology. She has extensive administrative experience of running large NIH awards as the founding PI of the Washington University St. Louis Digestive Disease Research Core Center (DDRCC) and was the PI of a UH2 Human Microbiome Demonstration Project involving multiple institutions (e.g. Stony Brook, Washington University St. Louis, U. of Colorado, U. of North Carolina and Mount Sinai). She relinquished being Director of the Washington University DDRCC shortly after successfully renewing the grant for a second round, and joined the Stony Brook University faculty in 10/2009 in order to join her family, who had already relocated to Stony Brook earlier that year. Since moving to Stony Brook University she began building a GI Biobank at Stony Brook that would parallel the operations of the Washington University St. Louis DDRCC Biobank. She was appointed Chief of the Division of Gastroenterology and Hepatology in July 2013 after serving as interim chief the previous year. She was nominated as one of three SUNY Presidential Fellows for the SUNY Health Network of Excellence, which is “an umbrella network that engages and maximizes the diverse strengths in biomedical research across the SUNY campuses.” The mission of SUNY Health to integrate assets in areas including “personalized medicine, “clinical research capacity to advance translational research”, are areas that are aligned with the target areas of PAR-14-152. Dr. Li has demonstrated the passion and tenacity required to bring this tri institutional partnership to fruition.

As Chief of the Division of Gastroenterology and Hepatology, Dr. Li communicates on a regular basis with Dr. Vincent Yang, who is Chairman of Medicine and Clinical Co-director of the SUNY Stony Brook Scholars in Biomedicine Program (see letter of support). As Director of Colon Cancer Screening in the Stony Brook Cancer Center, she communicates on a regular basis with Dr. Yusuf Hannun, Director of the Stony Brook Cancer Center (see letter of support). As Director of the Stony Brook GI Biobank module, she communicates on a regular basis with Dr. Kenneth Shroyer, Chairman of Pathology and Director of the Stony Brook Cancer Center Biobank (see letter of support).

She has extensive experience in mentoring trainees at various levels and junior faculty. She has served on the MSTP admissions committee and the MA MD admissions committee at Washington University-St. Louis. Under her leadership as founding Director of the Washington University-St. Louis DDRCC, she mentored many junior faculty in the DDRCC Pilot Program that have since gone on to become extremely successful principle investigators that are federally funded.

Dr. Li is a strong advocate for increasing diversity at academic medical centers. She was one of the founding members and past President of the Academic Women's Network at Washington University-St. Louis. She is a founding member of the newly formed Stony Brook University Women's Leadership Council which is aimed at mentoring exceptional Stony Brook women undergraduate students. Dr. Li has been actively involved with teaching and mentoring Stony Brook undergraduates, admitted through the Education Opportunities Program, who are interested in pursuing careers in health and biomedical research. She created the Chemistry Head Start Program during the pre-Freshman Summer Academy. She teaches a Freshman seminar each year for EOP students interested in pursuing careers in health and the biomedical sciences entitled “Sugar and Fat” which relate concepts they are learning in General Chemistry to the current epidemic of diabetes and obesity. Her contributions to the EOP were recognized in the 2012 Stony Brook University Education Opportunities Program/ Advancement on Individual Merit Distinguished Advocate Award. A major mark of this program's success is the matriculation of two EOP students to SUNY Stony Brook School of Medicine since 2013. These students are currently supported in part by scholarships donated to the university by Dr. Li and her husband Dr. Stanley, President of Stony Brook University.

**Moro O. Salifu, M.D. M.P.H., M.B.A.** (co-PI, SUNY Downstate): Dr. Salifu is co-PI for the Administrative Core and co-PI for the Training and Education Program. He is Professor of Medicine and Chief of Nephrology and Transplantation and Chair of the department of Medicine at SUNY Downstate Medical Center. He will work closely with Dr. Li in integrating the nascent SUNY Downstate GI Biobank with the SUNY Stony Brook GI Biobank. Dr. Salifu has outstanding administrative skills, including his role as the contact PI on the current Brooklyn Health Disparities Center P20. Research projects supported by the Brooklyn Health Disparities P20 currently focus on HIV and obstructive sleep apnea. This proposed P20 project aligns with but does not

duplicate the goals of the Brooklyn Health Disparities Center. Furthermore, Dr. Salifu has an outstanding track record as a researcher, educator and clinician all of which have resulted in numerous awards locally and nationally. An effective communicator, Dr. Salifu was initially appointed as Director of Transplant Nephrology in 2001, when he led successful efforts to expand the transplant program through efforts to increase awareness of kidney transplantation in the African-American community, a major area of health disparity. In 2003, he was appointed Director of the Nephrology Fellowship Training Program, responsible for nephrology in the main SUNY Downstate campus as well as in three major affiliated hospitals: Kings County Hospital Center, the Brooklyn VA Medical Center and Staten Island University Hospital. In this capacity, Dr. Salifu has trained and mentored many residents and fellows, across different institutions, a key and necessary experience required for the conduct of this proposal. He also served a two year term with commendation as the New York State representative to the Minority Affairs Committee of the United Network for Organ Sharing (UNOS) from 2005-2007. In 2008, Dr. Salifu was appointed Chief of Nephrology and Director of the Transplant Program. He consolidated both medical and surgical aspects of end stage renal disease (ESRD) care and led efforts to establish the first ESRD/Transplant Product Line, where two independent services now function as a unit with highly defined systems and processes. This has resulted in restructuring and expansion of both programs and better care to our predominantly African-American patient population. In 2010, he was the recipient of the SUNY Downstate Hospital Quality Award, reserved for individuals who have demonstrated exceptional capacity to influence the quality of care at Brooklyn's academic teaching hospital. His successful experience in bringing both medical professionals, clinical programs, and the patient communities to work together towards a common goal is a major strength that is invaluable for this Administrative Core.

**Joel Saltz, M.D.-Ph.D.** (co-Investigator, SUNY Stony Brook). Dr. Joel Saltz will spearhead the development of an integrative biomedical informatics platform for linking coded de-identified biospecimens archived with the Stony Brook or the nascent Downstate GI BioBank with clinical metadata and with downstream data generated from the biospecimens. He is the Cherith Professor and Founding Chair of the Biomedical Informatics Department at Stony Brook University, Associate Director of Stony Brook University Cancer Center and fellow of the American College of Medical Informatics. He also holds a secondary appointment in the Department of Pathology. His research focus is on development of methods to assemble a coherent biomedical picture by integrating information from multiple complementary microscopy, imaging and molecular data sources. The goal is to better predict outcome and response to treatments, generate basic insights into pathophysiology, and identify new treatment targets. Dr. Saltz has a long history of research and development of high performance infrastructures and frameworks for scientific research. He serves as PI on the NCI cooperative grant Tools to Analyze Morphology and Spatially Mapped Molecular Data, on two highly synergistic R01 grants involving integration of molecular and Pathology information. He has served as PI of a P20 NIBIB funded BISTI center dedicated to integrative Pathology and Radiology image analysis, as Program Director of the Emory In Silico Research Center for Excellence and led the Biomedical Informatics Programs in both Ohio State and the Emory CTSA. In September 2013, he became the Associate Director for Informatics for the Stony Brook Cancer Center with the highly synergistic goal of developing a thematic area that focuses on development of methods to generate and analyze integrative multi-scale, morphological/molecular cancer tissue characterizations and use of integrated characterizations to 1) better understand tumor stroma interactions, multi-clonality and tumor heterogeneity; 2) develop methods to leverage heterogeneity information for treatment planning and; 3) to better monitor and steer cancer treatments. He has spearheaded a variety of multi-disciplinary efforts that have led to the development of innovative tools and middleware components for the management, indexing, query, analysis, and integration of multi-scale biomedical data. He has led projects supported by a wide range of institutes and agencies including NCI, NLM, NIBIB, NSF, DARPA, AFOSR, NASA, DOD and DOE to develop innovative techniques, methodologies, algorithms and software systems to support large scale digital microscopy, high-performance computing, data management, and data federation over the past 25 years. Dr. Saltz has founded two graduate programs in biomedical informatics, one at Ohio State and the other at Emory; he is in the process of developing a highly synergistic MS/PhD program in Biomedical Informatics at Stony Brook.

#### P20 CSHL (Cancer Center) Administrative Core

**W. Richard McCombie, Ph.D.** (contact-PI, CSHL) is a Professor at CSHL and Scientific Director of the CSHL Genomics Shared Resource. Dr. McCombie has extensive experience as the PI on successful large multi-

institutional projects. He is currently the PI on two multi-institutional projects, one involving a foreign collaborator. He is a member of the CSHL Cancer Center. Dr. McCombie is also the CSHL contact PI for pilot project P1 in the P20 Cancer Research Program and the CSHL contact PI for the Training and Education Program.

**David Tuveson, M.D.- Ph.D.** (co-Investigator, CSHL) is Professor and Deputy Director of the CSHL Cancer Center and is the founding Director of the Cancer Therapeutics Initiative at CSHL - a preclinical therapeutic center designed to develop efficacious therapies and accurate diagnostics for cancer. In addition, he has developed clinical and industry liaisons to manage patient samples and coordinate relationships with hospital partners and pharmaceutical and biotechnology companies. Dr. Tuveson also serves as Director of the Lustgarten Foundation Pancreatic Research Laboratory at CSHL and as Director of Research for the Lustgarten Foundation. Dr. Tuveson is also the CSHL contact PI for pilot project P2 in the P20 Cancer Research Program.

#### **4. Administrative Management**

The fiscal and clerical management of the SUNY P20 award will be overseen by Dr. Li, the contact PI at SUNY Stony Brook in partnership with Dr. Moro Salifu, the co-PI at SUNY Downstate. Dr. Li will utilize the existing Stony Brook Cancer Center Administrative structure for assistance with administrative functions (fiscal, clerical management). This assistance was made available to her in the preparation of this grant application by Dr. Hannun, the Director of the Stony Brook Cancer Center. Should Dr. Li be unwilling or unable to continue to lead this award, she will be replaced by Dr. Patricia Thompson who is the SUNY contact PI for the Training and Education Program and Chair of the Internal Advisory Committee. Dr. Thompson and Dr. Li currently work closely as co-leaders of the GI Cancer Research Program in the Stony Brook Cancer Center. Dr. Thompson would relinquish her position as Chair of the Internal Advisory Committee and will be replaced by Dr. Vincent Yang, Simons Professor and Chair of the Department of Medicine.

The fiscal and clerical management of the CSHL P20 award will be overseen by Dr. McCombie, the contact PI at CSHL. He will utilize the existing Cancer Center Administrative structure at CSHL for CSHL specific, internal administrative functions (fiscal, clerical management) required for this program. This will include such activities as carrying out sequencing, which will be done at the Genomics Shared Resource. Dr. McCombie will thus serve as an important liaison with the Cancer Center Administration (CCA) at CSHL and the P20 Steering Committee. Should Dr. McCombie be unwilling or unable to continue to lead this award, he will be replaced by Dr. Tuveson, co-director of the CSHL Administrative Core.

Both Dr. Li and Dr. McCombie are committed to attend NCI sponsored meetings/workshops and other NCI-related activities. Dr. Li will commit 25% effort and Dr. McCombie will commit 10% effort towards the P20 project.

#### **5. Internal Advisory Committee:**

**Patricia Thompson, Ph.D.,** co-chair, SUNY Stony Brook. Dr. Thompson recently joined the faculty at Stony Brook University in the Department of Pathology as a Professor and as the Associate Director of Basic Science for the Stony Brook Cancer Center. Her research focus is on translating knowledge of breast and colorectal cancer biology to prevention of primary disease and metastasis in early stage patients. She has extensive experience successfully mentoring young investigators (undergraduate, pre and post-doctoral and early career faculty) and has taken a leadership role in multiple programs aimed at increasing diversity. In this P20 project she will also serve as the SUNY contact PI for the Training and Education program and she is extremely well qualified to monitor the progress of the two pilot projects **P1** and **P2** in the Cancer Research Program.

**Mark Stewart, M.D.-Ph.D.** member, SUNY, Downstate. Dr. Stewart is Dean of the School of Graduate Studies and Vice Dean for Research at SUNY Downstate. As Dean of the School of Graduate Studies he was instrumental in securing institutional funds to support two trainees in the Scholars in BioMedicine in Cancer Health Disparities we are proposing to launch as part of our P20 Training and Education Program. He is also well placed to advise on how to introduce new learning modules on Cancer Health Disparities into existing graduate studies curricula. As the Research Core Director for the Brooklyn Health Disparities Center, which is aimed at reducing health disparities among minorities and new immigrants to Brooklyn, he is well qualified to monitor the progress of the pilot projects P1 and P2 in the Cancer Research Program.

**Alea A. Mills, Ph.D.**, co-chair, CSHL. Dr. Alea Mills is Professor of the Watson School for Biological Sciences at CSHL and is Director of the NCI T32 CSHL Cancer Gene Discovery and Cancer Biology Postdoctoral Research Training Grant. Dr. Mills' research group used chromosome engineering to identify a tumor suppressor gene that had eluded investigators for three decades. The gene, called Chd5, was shown by Mills to regulate an extensive cancer-preventing network. The Mills lab uncovered how Chd5 acts as a tumor suppressor: It binds to a protein found within chromatin to turn specific genes on or off, halting cancer progression. Thus she is extremely well qualified to monitor the progress of the pilot projects P1 and P2 in the Cancer Research Program and to advise on the Training and Education Program.

**Michael Wigler Ph.D.**, member CSHL. Dr. Michael Wigler is Professor of the Watson School for Biological Sciences at CSHL. The Wigler lab studies human cancer focusing primarily on breast and prostate cancer. He has been engaged in collaborative clinical studies to discover mutational patterns predicting treatment response and outcome and the development of diagnostics to detect cancer cells in bodily fluids such as blood and urine. He has been at the forefront of developing and applying tools such as single-cell DNA and RNA analysis. Thus he is extremely well qualified to monitor the progress of the pilot projects P1 and P2 in the Cancer Research Program.

## **6. P20 External Advisory Board**

**John Carethers, M.D.** (Chair, P20 External Advisory Board). Dr. Carethers is the John G. Searle Professor of Internal Medicine and Chair, Department of Internal Medicine at the U. of Michigan School of Medicine. Dr. Carethers has expressed that he has a vested interest in the field of cancer disparities, with experience as PI of an active U01 and former co-PI of a U54 Comprehensive Cancer Center Partnership, Program Leader of the Reducing Cancer Disparities program at a comprehensive cancer center, and author of multiple publications regarding the approach to care and the biology of colorectal cancer among African Americans.

**Antonio Baines, Ph.D.** (member, P20 External Advisory Board). Dr. Baines is Associate Professor of Biology at the Cancer Research Program, Julius L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University. The overall focus of his cancer biology research program is to discover novel molecular targets in cancer, especially pancreatic cancer, which can be targeted by potential cancer therapeutics.

**Marilyn Fraser-White, M.D.** (member, P20 External Advisory Board). Dr. Fraser White is Deputy Executive Director for the Arthur Ashe Institute for Urban Health (<http://www.arthurasheinstitute.org/arthurashe/about/>). The Arthur Ashe Institute sponsors a Health Science Academy Pipeline which exposes URM students, beginning in middle school (6-12), to the health sciences in order to increase minority representation in the healthcare and health sciences fields. Dr. Fraser-White has been engaged in development and implementation of health disparities learning modules for high school students and was recently a recipient of the SUNY Downstate President's Health Disparities Grant to develop a Health Disparities curriculum for Community Based Organizations in Brooklyn.

## **7. Estimated Timeline for Initial Planning, Priority Setting, Implementation and Evaluation Stages.**

**7A. Initial Planning Stage.** We have made significant progress since the initial submission of this P20 planning grant application, in terms of initial planning for the joint SUNY-CSHL Cancer Research Program and the Training and Education Program.

**7A.1 Cancer Research Program.** Dr. Martello-Rooney who will direct the SUNY Downstate GI Biobank has secured IRB approval for collection of URM clinical colon cancer and pancreatic cancer samples for research at SUNY Downstate and has completed MTAs with SUNY Stony Brook and CSHL. Dr. Bucobo and Dr. Li have obtained approval from the Protocol Review and Monitoring Committee of SUNY Stony Brook Cancer Center and IRB approval for EUS guided FNB for the pancreatic organoid project (P2). By securing IRB approval at this point we anticipate little down time in implementing the research proposed in pilot projects P1 and P2 of our Cancer Research Program. We plan to assist Dr. Martello-Rooney in obtaining a New York State BioBank license, which is required for establishing a Tissue Bank in this state, since SUNY Stony Brook has completed this process. However obtaining the license will not delay collection of samples for P1 and P2

since these samples will be used shortly after they have been collected and consequently will not have been “banked”.

We anticipate that the initial planning of an integrated biomedical informatics platform, regardless of the software used, will require that SUNY Stony Brook and Downstate clinicians (gastroenterologists, surgeons, radiation oncologists and medical oncologists) and investigators reach consensus on the data elements (e.g. clinical endpoints) and controlled vocabulary to facilitate cross transfer of the clinical metadata. As far as possible we plan to adopt the elements and vocabulary used by other cooperative collection efforts. Currently the Stony Brook GI BioBank employs REDCap, but there are ongoing discussions within the Stony Brook Cancer Center on what software will be used. Dr. Thompson, co-chair of the Internal Advisory Committee is working closely with Dr. Saltz, co-Investigator on the SUNY Administrative Core and are playing important roles in making these decisions.

**7A.2 Training and Education Program.** Since the initial submission of this P20 planning grant the P20 leadership became intrigued with developing a program similar in concept to the HHMI “med into grad” program for graduate students at all three institutions, particularly since SUNY Stony Brook launched a pilot Scholars in BioMedical Sciences program two years ago. However thus far, no URM graduate students were accepted and none of the translational projects addressed Cancer Health Disparities. This led us to propose building an integrated Scholars in BioMedical Sciences in Cancer Health Disparities onto the existing infrastructure developed for the SUNY Stony Brook Scholars in BioMedical Sciences. For this reason we anticipate little down time in implementing the proposed Scholars in BioMedical Science in Cancer Health Disparities. We anticipate that establishing this program will prove to be an important recruiting tool for URM doctoral students at all three institutions.

We anticipate that if our P20 grant is awarded then most of the planning activities will center on increasing our mentorship capacity among established cancer research investigators, and developing new learning modules related to Cancer Health Disparities. We are hopeful that the proposed annual Symposium on Cancer Health Disparities will provide a forum where trainees, basic scientists, clinicians and community leaders could discuss approaches to increasing mentorship capacity. We are also hoping to adopt modules on Cancer Health Disparities developed for high school students and the community to be directed to more senior trainees and established cancer research investigators.

***7B. Priority Setting Stage*** The Steering Committee along with the Internal Advisory Committee will review progress of the two pilot projects in the Cancer Research Program and the Training and Education Program on a quarterly basis. The External Advisory Committee will meet annually to review progress. Based on these discussions resources may be shifted in years 2-4 towards new initiatives, based on progress or lack of progress, successful acquisition of additional extramural funding of some of the objectives of the Pilot Projects or the Training and education Programs. The monthly GI Cancer Research meetings and the annual Symposium on Cancer Health Disparities will provide the leadership with information of potential alternative pilot research projects that could be funded if larger research awards are secured for the existing pilot projects.

**7B.1 Cancer Research Program.** As discussed further in Pilot Project 1, we anticipate that Dr. Jennie Williams will be submitting as PI a collaborative R01 grant application that overlaps with some of the objectives in P1 of the P20 award, namely RNA-Sequencing and RBBS sequencing. If we are fortunate enough to have both her R01 and the P20 funded, we have already made plans for shifting the priority of the sequencing towards exome and possibly whole human genome sequencing. We may also consider shifting resources more towards developing new methods of conducting integrative analysis of multidimensional datasets.

Similarly if we are fortunate to secure additional extramural funding to support Pilot Project 2, we may shift resources towards exome sequencing and whole human genome sequencing comparing URM and nonURM organoids, or by piloting drug sensitivity testing in the tumor progression model Dr. Mackenzie will be

**7B.2 Teaching and Education Program.** If we are fortunate enough to obtain extramural funding of the Scholars in Biomedical Sciences in Health Disparities (currently funding will be provided by matching funds from SUNY Stony Brook and Downstate) we may shift priorities towards developing online learning modules on Cancer Health Disparities.

## ***7C. Implementation Stage***

## 7C.1 Cancer Research Program.

*7C.1a. Summary of Pilot Research Project 1 (P1).* Two SUNY medical campuses (SUNY Stony Brook and SUNY Downstate) serving underrepresented minority communities with cancer health disparities are partnering with the NCI designated Cancer Center at the Cold Spring Harbor Laboratory (CSHL) to evaluate biological and genetic differences in colorectal cancers that may link to differences in cancer incidence and outcome observed in racial and ethnic minorities. We plan to develop a SUNY Downstate GI BioBank that will greatly augment the representation of underrepresented minorities in the collection of biospecimens that will use the same standard operating procedures currently in place at the SUNY Stony Brook GI BioBank. Furthermore the clinical metadata elements collected at SUNY Downstate will be the same and utilize a common controlled vocabulary that is used by the SUNY Stony Brook GI BioBank. To increase community participatory research among racial and ethnic minority populations, we plan to leverage the resources and expertise of the SUNY Downstate Brooklyn Health Disparities Center (led by Dr. Moro Salifu) in developing community education and outreach programs in underserved communities with a high proportion of racial and ethnic minorities (>70% African Americans). In P1, we propose to generate genomic and epigenetic profiling data of colon cancers using the NCI supported CSHL Shared DNA Sequencing Shared Resource Core directed by Dr. Dick McCombie (CSHL contact PI for P1). Generating the sequencing data will provide immediate feedback to the Downstate GI BioBank with respect to monitoring Q/A for their collection efforts. This genomic and epigenomic data will be linkable to parallel microRNA and RNA-Seq mRNA profiling and immunohistochemical data generated on the same coded deidentified samples by Dr. Jennie Williams (SUNY contact PI for P1) [13]. We anticipate that making the linked datasets available on the integrated biomedical informatics platform being developed by this proposed P20 project will facilitate sharing of these extremely valuable datasets with the larger cancer research community.

*7C.1b. Summary of Pilot Research Project 2 (P2).* We propose to test the hypothesis that genetic and gene expression alterations underlie the increased incidence, mortality, and treatment resistance observed in underrepresented minorities (URMs). A new tissue model system, organoids, will allow the evaluation of the cell autonomous contribution to the increased risk of pancreatic cancer in URM. This hypothesis will be tested by 1.) Establishing a cohort of URM pancreatic tumor organoids from endoscopic ultrasound guided fine needle core biopsy samples obtained at SUNY Downstate using procedures developed between SUNY Stony Brook and CSHL. 2.) Performing next generation sequencing (RNA and DNA sequencing) on the URM organoids to delineate the molecular properties of the organoids. This data will be compared with data obtained on non-URM organoids generated by a collaboration between SUNY Stony Brook and CSHL funded by separate funding sources. 3.) Determining whether there are innate cell biological differences between URM and non-URM organoids after measuring tumor progression in an orthotopic transplant model conducted at SUNY Stony Brook.

7C.2 Training and Education Program. We propose to address critical research and translation gaps for Cancer Health Disparities (CHD) by leveraging our strengths through a unique 'Scholars in Biomedical Sciences for CHDs' program (SBMS-CHD). The overarching goal and we believe a major solution to address CHDs is to successfully train PhD and MD/PhD scientists in cancer research that integrates concepts of research translation from the 'bench-to-bedside' academic model to cancer care delivery in community practice. The specific goal of this planning period will be to develop and test the effectiveness of a training environment aimed at enhancing knowledge of CHDs among established faculty mentors and to engage and empower, through knowledge and training in CHDs, a cohort of exceptional cancer research scientists with an interest in conducting high-quality research aimed at addressing biological and clinical causes of CHDs.

## **7D. Evaluation Stage**

7D.1 Cancer Research Program. We will monitor the number of manuscripts published using the preliminary data generated in the pilot research projects as well as the number of extramural awards generated using the preliminary data generated in the pilot research grants

7D.2 Training and Education Program (TEP). The TEP Leadership team will work closely with the SBMS Director and Clinical-Codirector (Drs. Tsirkas and Yang) to track the professional careers of the SBMS-CHD trainees after they graduate and receive their certificate for the SBMS-CHD program. We will monitor

publications and presentations, completion of the graduate program, entry into postdoctoral programs, new and early employment and success in competing for extramural funding. The development of the SBMS-CHD alumni group, will be very helpful for tracking as we invite alumni of the SBMS-CHD program to participate or possibly speak at the annual Cancer Health Disparities Symposium sponsored by the TEP.

## ADMINISTRATIVE CORE - REFERENCES

1. Descants C, Naishadham, Jemal A Cancer statistics for African Americans, 2013. *CA Cancer J Clin* 2013;63:151-166
2. Lee W, Nelson R, Mailey B, et al. (2012) Socioeconomic factors impact colon cancer outcomes in diverse patient populations. *J. Gastrointest Surg* 16:692-704.
3. Laiyemo AO, Doubeni C, Pinsky PF et al. (2010) Race and colorectal cancer disparities: health care utilization vs. different cancer susceptibilities. *J Natl Cancer Inst.* 102: 538-46.
4. Wallace K, Hill EG Lewin DN, et al. Racial disparities in advanced stage colorectal cancer survival. *Cancer Causes Control* 2013; 24:463-71.
5. National Cancer Institute. A snapshot of pancreatic cancer.  
<http://www.cancer.gov/researchandfunding/snapshots/pdf/Pancreatic-Snapshot.pdf>
6. Ries LAG, Melbert D, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2005. In Edwards BK, editor. National Cancer Institute; Bethesda MD: 2008.
7. Shavers VL, Harlan LC, Jackson M, et al. racial/ethnic patterns of care for pancreatic cancer. *J. Palliat Med* 2009; 12:623-630. PMC2925034
8. Chang KJ, Parasher G, Christie C, et al Risk of pancreatic adenocarcinoma: disparity between African Americans and other racial/ethnic groups. *Cancer* 2005; 103:349-57.
9. Cancer Genome Atlas Network Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012; 487: 330-337. PMC3401966
10. Shavers VL, Fagan P, Lawrence D, et al. Barriers to racial/ethnic minority application and competition for NIH research funding. *J Natl Med Assoc* 2005; 97: 1005-63.
11. Xu X, Zhang Y, Williams J, et al. Parallel comparison of Illumina RNA-Seq and Affymetrix microarray platforms on transcriptomic profiles generated from 5-aza-deoxy-cytidine treated HT-29 colon cancer cells and simulated datasets. *BMC Bioinformatics* 2013; 14 Suppl 9:S1. PMC3697991
12. Son P, Lane DS, Messina CR, Yang J, Zhu J, et al. Impact of Project SCOPE on racial/ethnic disparities in colorectal cancer screening. *J. Racial and Ethnic Health Disparities.* 2014; 1: 110-19.
13. Li E, Ji P, Ouyang N, Zhang Y, Wang XY, et al. Differential expression of miRNAs in colon cancer between African and Caucasian Americans: implications for cancer racial health disparities. *Int J. Oncol*, 2014; 45:587-94 PMC4091964



Joel H. Saltz, MD, PhD  
Cherith Professor and Founding Chair, Department of Biomedical Informatics  
Vice President for Clinical Informatics, Stony Brook Medicine  
Associate Director, Stony Brook University Cancer Center

March 16, 2015

Ellen Li, MD, PhD  
Division Chief, Gastroenterology and Hepatology  
Professor, Department of Medicine  
Health Sciences Center T17, Room 06  
Stony Brook University  
Stony Brook, NY 11794

RE: PAR-14-152, "Feasibility Studies to Build Collaborative Partnerships in Cancer Research (P20)"

Dear Dr. Li:

I am writing to convey my support of and participation in your grant application, "Feasibility Studies to Build Collaborative Partnerships in Reducing Racial/Ethnic Disparities in GI Cancer Research."

As you are aware, we are planning the SBU Biomedical Informatics Core as a shared resource to achieve the following aims:

**Aim 1: Develop and deploy a suite of interoperable systems, which will manage various data types commonly used in Stony Brook Clinical and Biomedical studies.** These systems will include specialized repositories of clinical information, specimen information systems, research PACS, virtual slide databases, i2b2 and REDCap. In collaboration with Stony Brook IS, we will leverage and adapt the Cerner Healthe Intent population health platform to generate an i2b2 based data warehouse populated with clinical phenotype data derived from Stony Brook Healthcare electronic health record data.

**Aim 2: Develop an integrative clinical phenotype warehouse.** We will specify and enable the use of common data elements and semantic knowledge models across Stony Brook projects and data sources. A rich set of interdisciplinary projects at Stony Brook share the common need for integrative analytics. We are integrating information from multiple complementary datatypes

Dr. Ellen Li  
March 16, 2015  
Page 2

including billing codes, laboratory data, medication data and natural language-analyzed discharge summaries, nursing notes, Radiology and Pathology reports to generate clinical phenotype information. This work leverages a variety of machine learning and predictive modeling tools and algorithms.

**Aim 3: Develop data exploration tools.** These tools are designed to support interactive data exploration and query. These flexible, customizable tools will play a crucial role in developing the integrative data products described in Aim 2 and in supporting analysis of relationships between clinical phenotype and molecular data. These tools make it possible to compare, integrate, visualize and analyze combinations of public and private data sources.

**Aim 4: Develop IRB approved de-identification pipelines.** In collaboration with Stony Brook IS, we will adapt and develop tools to generate fully de-identified, data shifted datasets, limited datasets along with IRB umbrella protocols, data use agreements and IRB approved review procedures to govern data access and use.

**Aim 5: Comprehensive set of activities to engage, assist, and train investigators so that they can make full use of Biomedical Informatics Shared Resource tools and incorporate informatics into their research.** These activities will include coordinated consultation sessions, investigator-centered system design processes, and training on principles of biomedical informatics and use of informatics tools in research via several existing and in-development educational programs.

If you have any questions, please feel free to contact me. I look forward to leading BMI's participation in this project.

Sincerely,

A handwritten signature in black ink, appearing to read "Joel H. Saltz". The signature is fluid and cursive, with the first name "Joel" and last name "Saltz" clearly distinguishable.

Joel H. Saltz



A Diverse Legacy, A Bright Future

College of Medicine  
College of Nursing  
College of Health Related Professions  
School of Graduate Studies  
School of Public Health

## Department of Medicine

February 27, 2015

Li Ellen, MD  
Chief, Division of Gastroenterology and hepatology  
STONY BROOK MEDICINE

Re: RE: **Feasibility Studies to Build Collaborative Partners in Cancer Research**

Dear Ellen,

I am delighted writing this letter of support for your proposal entitled '**Partnership to Study Racial/Ethnic differences in GI cancer Biology**'. This translational research proposal is significant and addresses a knowledge gap in GI cancers in ethnic minorities in the United States.

As Chair of Medicine at Downstate and also director of the Brooklyn Health Disparities Center, I have the resources available to me to support this effort and to ensure that the collaboration between our two campuses succeeds. The success of this proposal for which I have no doubt, will demonstrate good scientific collaborative efforts between our two campuses and sets the foundation for extensive collaborative translational work beyond our two campuses to involve the rest of the SUNY medical campuses. The exchange of samples and other aims in the project will support multiple projects in preparation for large federal grants focused on health disparities in GI cancers and to improve research opportunities for SUNY undergraduate students in this area.

Given your experience and reputation in this field, coupled with our current work, I believe we are well-poised to execute this grant. I will be fully dedicated and will ensure timely and efficient conduct of this study and look forward to the initiation of this exciting project.

With best regards,

A handwritten signature in black ink, appearing to read 'MSALIFU'.

Moro O. Salifu, MD, MPH  
Professor & Chair, Department of Medicine  
SUNY, Downstate Medical Center, Brooklyn, NY 11203  
Tel; (718) 270-2030  
Email: moro.salifu@downstate.edu



# SUNY DOWNSTATE Medical Center

College of Health Related Professions

## MEDICAL INFORMATICS PROGRAM

University Hospital of Brooklyn

College of Medicine

School of Graduate Studies

College of Nursing

College of Health Related Professions

March 11, 2015

To whom it may concern,

It is a pleasure for me to agree to participate in the P20 grant entitled "Feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research". As a biomedical informatician I will collaborate with Dr. Joel Saltz, chair of the department of biomedical informatics of Stony Brook University, in planning the informatics services and structures necessary to combine electronic health record data with the genomic data generated, to create the bioinformatics. This may also be in coordination with the SUNY Health Network of Excellence Project called the Clinical Integrated Data Repository (CIDR), of which I am the Downstate local PI. CIDR is a project to examine the feasibility of combining electronic health records across all the SUNY medical campuses, to create a larger repository for research. My prior experience with cancer research includes work with Dr. Sherri Sheinfeld Gorin on colorectal and prostate cancer detailing. Prior work with large data repositories for research includes graduate training at Columbia university and use of its large clinical data repository, as well as serving on its Clinical and Translational Science Award informatics committee, with a charge to foster inter-and cross-institutional as well as multidisciplinary collaboration.

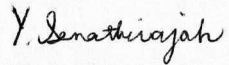
My role will be to plan and facilitate the data acquisition, cleaning, and related informatics work at Downstate so that this data can be stored and/or connected with the data in the repositories being created by Stony Brook under the leadership of Joel Saltz. These systems will include specialized repositories of clinical information, specimen information systems, research PACS, virtual slide databases, i2b2 and REDCap, to generate an i2b2 based data warehouse. This includes an **integrative clinical phenotype warehouse**, integrating information from multiple complementary datatypes including billing codes, laboratory data, medication data and natural language-analyzed discharge summaries, nursing notes, Radiology and Pathology reports to generate clinical phenotype information. It also includes flexible, customizable **data exploration tools**. These tools are designed to support interactive data exploration and querying. Finally, it will include a comprehensive set of activities to engage, assist, and train U20 investigators so that they can make full use of Biomedical Informatics Shared Resource tools and incorporate informatics into their research. These activities will include coordinated consultation sessions, investigator-centered system design processes, and training on principles of biomedical informatics and use of informatics tools.

This P20 project is noteworthy as it will set up the resources to reveal much about cancer disparities. SUNY Downstate Medical Center is located in a minority, low-income, medically underserved community in Brooklyn, NY, and thus will provide important records enabling us to examine the causes of disparities as noted in the research plan. As a majority (~85%) of

master's-level informatics students at Downstate are minorities, the project will also provide opportunities for informatics training for minority students.

This project is a well-designed collaboration between three institutions with leading expertise in different areas; I expect it will be very fruitful. I am happy to take part.

Sincerely,

A handwritten signature in cursive script, reading "Y. Senathirajah".

Yalini Senathirajah

Assistant Professor  
Department of Medical Informatics  
347-619-4021

## APPLICATION FOR FEDERAL ASSISTANCE

**SF 424 (R&R)****5. APPLICANT INFORMATION****Organizational DUNS\*:** 8048782470000

Legal Name\*: The Research Foundation for SUNY, Stony Brook University  
 Department: Office of Sponsored Programs  
 Division: OVPR  
 Street1\*: STONY BROOK UNIVERSITY  
 Street2: The Office of Sponsered Programs  
 City\*: STONY BROOK  
 County:  
 State\*: NY: New York  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 117940000

Person to be contacted on matters involving this application

Prefix: First Name\*: Middle Name: Last Name\*: Suffix:  
 Ms. Andria  
 Position/Title: Grant Administrator  
 Street1\*: W5510 Melville Library  
 Street2: Stony Brook University  
 City\*: Stony Brook  
 County: Suffolk  
 State\*: NY: New York  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 117943362  
 Phone Number\*: 631 632-1610 Fax Number: 631 632-6963 Email: andria.adler@stonybrook.edu

**7. TYPE OF APPLICANT\***

X: Other (specify)

Other (Specify): Non Profit

**Small Business Organization Type**☐ Women Owned☐ Socially and Economically Disadvantaged**11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT\***

Pilot Project Research Project 1

**12. PROPOSED PROJECT**

Start Date\* Ending Date\*  
 09/01/2015 08/31/2019

**Project/Performance Site Location(s)****Project/Performance Site Primary Location**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY, Stony Brook University  
Duns Number: 8048782470000  
Street1\*: STONY BROOK UNIVERSITY  
Street2: The Office of Sponsered Programs  
City\*: STONY BROOK  
County:  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 117940000  
Project/Performance Site Congressional District\*: NY-001

---

**Project/Performance Site Location 1**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY, Downstate Medical Center  
DUNS Number: 0407963280000  
Street1\*: 450 Clarkson Avenue  
Street2:  
City\*: Brooklyn  
County:  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 112030000  
Project/Performance Site Congressional District\*: NY-009

---

File Name

**Additional Location(s)**

## RESEARCH &amp; RELATED Other Project Information

<b>1. Are Human Subjects Involved?*</b> <input checked="" type="radio"/> Yes <input type="radio"/> No 1.a. If YES to Human Subjects Is the Project Exempt from Federal regulations? <input type="radio"/> Yes <input checked="" type="radio"/> No If YES, check appropriate exemption number:    — 1 — 2 — 3 — 4 — 5 — 6 If NO, is the IRB review Pending? <input type="radio"/> Yes <input type="radio"/> No IRB Approval Date: Human Subject Assurance Number	
<b>2. Are Vertebrate Animals Used?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No 2.a. If YES to Vertebrate Animals Is the IACUC review Pending? <input type="radio"/> Yes <input type="radio"/> No IACUC Approval Date: Animal Welfare Assurance Number	
<b>3. Is proprietary/privileged information included in the application?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
<b>4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No 4.b. If yes, please explain: 4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? <input type="radio"/> Yes <input type="radio"/> No 4.d. If yes, please explain:	
<b>5. Is the research performance site designated, or eligible to be designated, as a historic place?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No 5.a. If yes, please explain:	
<b>6. Does this project involve activities outside the United States or partnership with international collaborators?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No 6.a. If yes, identify countries: 6.b. Optional Explanation:	
<b>7. Project Summary/Abstract*</b>	Filename P1_ABSTRACT_Final.pdf
<b>8. Project Narrative*</b>	P1_Narr_F.pdf
<b>9. Bibliography &amp; References Cited</b>	Pilot_1_References_Final.pdf
<b>10. Facilities &amp; Other Resources</b>	
<b>11. Equipment</b>	

**ABSTRACT – PILOT RESEARCH PROJECT 1 (P1)**

Two SUNY medical campuses (SUNY Stony Brook and SUNY Downstate) serving underrepresented minority communities with cancer health disparities are partnering with the NCI designated Cancer Center at the Cold Spring Harbor Laboratories (CSHL) to evaluate biological and genetic differences in colorectal cancers that may link to differences in cancer incidence and outcome observed in racial and ethnic minorities. We plan to develop a SUNY Downstate GI BioBank that will greatly augment the representation of underrepresented minorities in the collection of biospecimens that will use the same standard operating procedures currently in place at the SUNY Stony Brook GI BioBank. Furthermore the clinical metadata elements collected at SUNY Downstate will be the same and utilize a common controlled vocabulary that is used by the SUNY Stony Brook GI BioBank. To increase community participatory research among racial and ethnic minority populations, we plan to leverage the resources and expertise of the SUNY Downstate Brooklyn Health Disparities Center (led by Dr. Moro Salifu) in developing community education and outreach programs in underserved communities with a high proportion of racial and ethnic minorities (>70% African Americans). In **P1**, we propose to generate genomic and epigenetic profiling data of colon cancers using the NCI supported CSHL Shared DNA Resource Core directed by Dr. **Dick McCombie** (CSHL contact PI for **P1**). Generating the sequencing data will provide immediate feedback to the Downstate GI BioBank with respect to monitoring Q/A for their collection efforts. This genomic and epigenomic data will be linkable to parallel microarray and RNA-Seq data generated on the same coded deidentified samples by Dr. **Jennie Williams** (SUNY contact PI for **P1**). We anticipate that making the linked datasets available on the integrated biomedical informatics platform being developed by this proposed P20 project will facilitate sharing of these extremely valuable datasets with the larger cancer research community.

## **Project Narrative**

In the US, individuals of African descent are at higher risk for developing GI cancers (colorectal and pancreatic) and also exhibit higher mortality rates for these cancers compared to individuals of Caucasian descent. This grant will serve to build an integrative partnership between two SUNY medical campuses, Stony Brook and Downstate, and the NCI-designated Cancer Center at Cold Spring Harbor Laboratories to study racial and ethnic differences in GI cancer biology.

Along with community education and outreach programs, this partnership will improve our ability to collect the under-represented minority (URM) biospecimens that are critical for research addressing the disparity of URM populations and GI cancers. By integrating the education and training resources of these three institutions, we will increase the recruitment of students and investigators from cancer health disparity populations for training in translational research and emerging technologies.

## RESEARCH &amp; RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator				
Prefix:	First Name*: Ellen	Middle Name	Last Name*: Li	Suffix:
Position/Title*:	Chief			
Organization Name*:	The Research Foundation for SUNY, Stony Brook University			
Department:	Medicine			
Division:	Gastroenterology Hepatology			
Street1*:	101 Nicolls Road Heath Science Center			
Street2:	T-17 Room 060			
City*:	Stony Brook			
County:	Suffolk			
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117948173			
Phone Number*:	631-444-2119	Fax Number:	631-444-8886	E-Mail*: ellen.li@stonybrook.edu
Credential, e.g., agency login: ELLENLI1				
Project Role*: Other (Specify)		Other Project Role Category: Project Lead		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:				
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Jennie	Middle Name	Last Name*: Williams	Suffix:
Position/Title*:	Research Asst Professor of Medicine			
Organization Name*:	The Research Foundation for SUNY, Stony Brook University			
Department:	Medicine			
Division:	Cancer Prevention			
Street1*:	Stony Brook University			
Street2:	T17-080			
City*:	Stony Brook			
County:	Suffolk			
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117948175			
Phone Number*:	631-444-9539	Fax Number:	631-444-9553	E-Mail*: jennie.williams@stonybrook.edu
Credential, e.g., agency login: jenniewilliams				
Project Role*: Co-Investigator			Other Project Role Category:	
Degree Type:			Degree Year:	
Attach Biographical Sketch*:			File Name	
			Williams_P20Biosketch_31515.pdf	
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Paula	Middle Name I	Last Name*: Denoya	Suffix:
Position/Title*:	Assistant Professor of Surgery			
Organization Name*:	The Research Foundation for SUNY, Stony Brook University			
Department:	Medicine			
Division:	Surgery			
Street1*:	Stony Brook University			
Street2:	HSC 18-46 b			
City*:	Stony Brook			
County:	Suffolk			
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117940000			
Phone Number*:	631-444-3431	Fax Number:		E-Mail*: paula.denoya@stonybrookmedicine.edu
Credential, e.g., agency login: PDENOYA				
Project Role*: Co-Investigator			Other Project Role Category:	
Degree Type:			Degree Year:	
Attach Biographical Sketch*:			File Name	
			DenoyaNIHbiosketch2015.pdf	
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Moro	Middle Name	Last Name*: Salifu	Suffix:
Position/Title*:	Director, Nephrology Fellowship Program			
Organization Name*:	The Research Foundation for SUNY, Downstate Medical Center			
Department:	Medicine			
Division:	Nephrology			
Street1*:	450 Clarkson Ave			
Street2:				
City*:	Brooklyn			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	112030000			
Phone Number*:	718-270-1584	Fax Number:	E-Mail*: moro.salifu@downstate.edu	
Credential, e.g., agency login: morosalifu				
Project Role*: Other (Specify)		Other Project Role Category: Subsite Lead		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:				
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Laura	Middle Name	Last Name*: Martello-Rooney	Suffix:
Position/Title*:	Director of GI Research			
Organization Name*:	The Research Foundation for SUNY, Downstate Medical Center			
Department:	Medicine			
Division:	GI Research			
Street1*:	450 Clarkson Ave			
Street2:				
City*:	Brooklyn			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	112032012			
Phone Number*:	718-270-1290	Fax Number:	718-270-7201	E-Mail*: laura.martello-rooney@downstate.edu
Credential, e.g., agency login: MARTELLOROONEY				
Project Role*: Other (Specify)		Other Project Role Category: Subsite Co-Investigator		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:				
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Mark	Middle Name	Last Name*: Stewart	Suffix:
Position/Title*:	Prof of Physiology Pharmacology, and Neurolog			
Organization Name*:	The Research Foundation for SUNY, Downstate Medical Center			
Department:				
Division:	Graduate Studies			
Street1*:	450 Clarkson Ave			
Street2:				
City*:	Brooklyn			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	112030000			
Phone Number*: (718) 270-1167	Fax Number: (718) 270-3103	E-Mail*: mark.stewart@downstate.edu		
Credential, e.g., agency login: mstewart				
Project Role*: Other (Specify)		Other Project Role Category: Subsite Co-Investigator		
Degree Type: MD,PHD,BS		Degree Year:		
		File Name		
Attach Biographical Sketch*:				
Attach Current & Pending Support:				

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2015

End Date\*: 08-31-2016

Budget Period: 1

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Jennie		Williams		Co-Investigator	135,860.00	0.6			6,793.00	3,865.00	10,658.00
2.	Paula		DeNoya		Co-Investigator	0.00	0.24			0.00	0.00	0.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	10,658.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							10,658.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
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2. Foreign Travel Costs	0.00
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<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
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2. Stipends	0.00
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3. Travel	0.00
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4. Subsistence	0.00
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5. Other:	
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<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	2,500.00
2. Publication Costs	500.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	20,688.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
<b>Total Other Direct Costs</b>	<b>23,688.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>34,346.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. ModifiedTotal Direct Cost	58.0	13,658.00	7,922.00
2. DownState	61.5	10,688.00	6,573.00
	<b>Total Indirect Costs</b>		<b>14,495.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 2/1/13 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl. W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>48,841.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: Project_1.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 2

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2016

End Date\*: 08-31-2017

Budget Period: 2

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Jennie		Williams		Co-Investigator	135,860.00	0.6			6,793.00	3,865.00	10,658.00
2.	Paula		DeNoya		Co-Investigator	0.00	0.24			0.00	0.00	0.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	10,658.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							10,658.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	2,500.00
2. Publication Costs	500.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	13,717.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
<b>Total Other Direct Costs</b>	<b>16,717.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>27,375.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. ModifiedTotal Direct Cost	58.0	16,158.00	9,372.00
2. DownState MTDC	61.5	13,717.00	8,436.00
	<b>Total Indirect Costs</b>		<b>17,808.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 2/1/13 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl. W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>45,183.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: Project_1.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 3

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 3

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Jennie		Williams		Co-Investigator	135,860.00	0.6			6,793.00	3,865.00	10,658.00
2.	Paula		DeNoya		Co-Investigator	0.00	0.24			0.00	0.00	0.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	10,658.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							10,658.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	2,500.00
2. Publication Costs	500.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	13,737.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. none	0.00
<b>Total Other Direct Costs</b>	<b>16,737.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>27,395.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. ModifiedTotal Direct Cost	58.0	16,158.00	9,372.00
2. Downstate MTDC	61.5	13,737.00	8,448.00
	<b>Total Indirect Costs</b>		<b>17,820.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 2/21/2014 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl. W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>45,215.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: Project_1.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 4

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 4

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Jennie		Williams		Co-Investigator	135,860.00	0.6			6,793.00	3,865.00	10,658.00
2.	Paula		DeNoya		Co-Investigator	0.00	0.24			0.00	0.00	0.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	10,658.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							10,658.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:**    ☒ Project    ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:**    File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
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2. Foreign Travel Costs	0.00
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<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
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2. Stipends	0.00
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3. Travel	0.00
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4. Subsistence	0.00
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5. Other:	
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<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 4

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	2,500.00
2. Publication Costs	500.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	13,737.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. none	0.00
<b>Total Other Direct Costs</b>	<b>16,737.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>27,395.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. ModifiedTotal Direct Cost	58.0	16,158.00	9,372.00
2. DownState MTDC	61.5	13,737.00	8,448.00
	<b>Total Indirect Costs</b>		<b>17,820.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 2/21/2014 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl. W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>45,215.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: Project_1.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## Budget Justification – Pilot Project P1 (Institutional)

### A. Key Personnel:

1. **Jennie Williams, Ph.D.** Contact PI. **Dr. Williams** will devote 0.6 calendar months to this project at her salary and fringes. Dr. Jennie Williams is an URM NIH funded investigator currently seeking to submit her competitive renewal of her RO1. She is Associate Professor of Preventive Medicine. In 2010, initiated a project to test the hypothesis that differential expression of microRNAs in African American colon cancers could contribute to disparities in colon cancer outcome. With the support of the Stony Brook GI Biobank, directed by **Dr. Li**, she has identified and acquired African American and Caucasian colorectal tumor and adjacent nontumor tissue samples and gained access to African American and Caucasian colorectal tumor and adjacent nontumor tissue samples from the Washington University Siteman Cancer Center Tissue Procurement Facility and has recently published her results demonstrating increased expression of miR-182 in African American colon cancer tumors. In collaboration with **Dr. Dick McCombie** at CSHL she and **Dr. Denoya** have generated parallel RNA-Seq mRNA data and more recently have worked out the pipeline for generating parallel reduced representation bisulfite sequencing data from the Washington University Cancer Center samples. Unfortunately the Washington University samples is the limited clinical metadata linked to the samples and the inability to acquire additional clinical data (e.g. smoking, BMI, diabetes, and other potential confoundgin variable. Over the, past year, **Dr. Williams** has initiated a collaboration with Dr. **Laura Martello-Rooney** at SUNY Downstate and thus acquired an additional 75 African American colon cancer FFPE tissue samples for the microRNA studies. Dr. Williams and her staff assist with the collection of colorectal cancer specimens for the SUNY Stony Brook GI Biobank. **Dr. Williams** and **Dr. Li** will work closely both with **Dr. Martello-Rooney** and **Dr. McCombie** in planning the development of a parallel SUNY Downstate Biobank using standard operating procedures for sample collection, processing and transport of samples.
2. **Paula Denoya, M.D.** co-I. **Dr. Denoya** will devote 0.24 calendar months of uncompensated effort to this project. She is Assistant Professor of General Surgery in the Division of Colorectal Surgery. In 2010, she successfully competed for a Stony Brook School of Medicine Targeted Research Opportunity (TRO) Fusion award to collect epigenetic profiling data in clinical samples of colorectal cancers, in collaboration with **Dr. Dick McCombie** at CSHL. Their initial plan was to apply a hybrid capture method of mapping the methylation changes, which had been recently developed at CSHL to clinical samples. In order to design the array for the hybrid capture it was necessary to first survey the mRNAs that are expressed in normal colonic mucosa and colon cancers. As the technology for high resolution mapping of methylation evolved during the course of this project, **Dr. McCombie** advised **Dr. Denoya** to use reduced representation bisulfite sequencing (RRBS) for epigenetic profiling of her samples. **Dr. Denoya's** project thus laid the groundwork for demonstrating that we could generate high quality RNA-Seq data from clinical samples and developing the parameters for conducting RRBS at the Cold Spring Harbor Laboratories over the past three years. **Dr. Denoya** plays a very active role in colon cancer tissue sample collection and in phenotyping of the patient samples and is therefore critical to the success of the Stony Brook GI Biobanking effort.

**B. Other Personnel:** none

**C. Equipment:** none.

**D. Supplies:** \$2,500 is requested to cover the costs molecular biological reagents.

**E. Travel:** none

### F. Other Expenses:

Publications: \$500

Subcontract: \$ 20,637 is requested in direct costs from SUNY Downstate for pilot project **P1**.

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	Totals (\$)	
Section A, Senior/Key Person		42,632.00
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		42,632.00
Section C, Equipment		0.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		73,879.00
1. Materials and Supplies	10,000.00	
2. Publication Costs	2,000.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	61,879.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	0.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		116,511.00
Section H, Indirect Costs		67,943.00
Section I, Total Direct and Indirect Costs (G + H)		184,454.00
Section J, Fee		0.00

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2015

End Date\*: 08-31-2016

Budget Period: 1

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Laura		Martello-Rooney		Co-Investigator	65,000.00	0.6			3,250.00	1,438.00	4,688.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	4,688.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							4,688.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
1. Sub Zero Freezer	10,000.00

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>10,000.00</b>
------------------------	------------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
2. Foreign Travel Costs	0.00

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other:	

<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	2,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Trainee Field Work Costs	4,000.00
<b>Total Other Direct Costs</b>	<b>6,000.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>20,688.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Direct Total Cost	61.5	10,688.00	6,573.00
<b>Total Indirect Costs</b>			<b>6,573.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 1/31/13 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>27,261.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	
	File Name: P20_grant- Budget_justification_Pilot_Project_1_2015.pdf (Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 2

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2016

End Date\*: 08-31-2017

Budget Period: 2

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Laura		Martello-Rooney		Co-Investigator	65,000.00	0.6			3,250.00	1,467.00	4,717.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:

File Name:

Total Senior/Key Person

4,717.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
						Total Salary, Wages and Fringe Benefits (A+B)	4,717.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
--------------------------	-------------

**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	5,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Trainee Field Work Costs	4,000.00
<b>Total Other Direct Costs</b>	<b>9,000.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>13,717.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Direct Total Cost	61.5	13,717.00	8,436.00
<b>Total Indirect Costs</b>			<b>8,436.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 1/31/13 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>22,153.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	
	File Name: P20_grant- Budget_justification_Pilot_Project_1_2015.pdf (Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 3

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project    ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 3

**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Laura		Martello-Rooney		Co-Investigator	65,000.00	0.6			3,250.00	1,487.00	4,737.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												
<b>Additional Senior Key Persons:</b> File Name:											<b>Total Senior/Key Person</b>	<b>4,737.00</b>

**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
<b>0</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>0.00</b>
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>							<b>4,737.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
------------------------------------------------------------------------	------

2. Foreign Travel Costs	0.00
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<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
----------------------------------	------

2. Stipends	0.00
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3. Travel	0.00
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4. Subsistence	0.00
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5. Other:	
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<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	5,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Trainee Field Work Costs	4,000.00
<b>Total Other Direct Costs</b>	<b>9,000.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>13,737.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Direct Total Cost	61.5	13,737.00	8,448.00
<b>Total Indirect Costs</b>			<b>8,448.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 1/31/13 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>22,185.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	<b>File Name: P20_grant-</b>
	Budget_justification_Pilot_Project_1_2015.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 4

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 4

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Laura		Martello-Rooney		Co-Investigator	65,000.00	0.6			3,250.00	1,487.00	4,737.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	4,737.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							4,737.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
------------------------------------------------------------------------	------

2. Foreign Travel Costs	0.00
-------------------------	------

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
----------------------------------	------

2. Stipends	0.00
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3. Travel	0.00
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4. Subsistence	0.00
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5. Other:	
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<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 4

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	5,000.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Trainee Field Work Costs	4,000.00
<b>Total Other Direct Costs</b>	<b>9,000.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>13,737.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Direct Total Cost	61.5	13,737.00	8,448.00
<b>Total Indirect Costs</b>			<b>8,448.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 1/31/13 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>22,185.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: P20_grant- Budget_justification_Pilot_Project_1_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## **Feasibility Studies to Build Collaborative Partnerships in Cancer Research (P20)**

### **Feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research**

#### **BUDGET JUSTIFICATION – Pilot Project 1**

##### **PERSONNEL**

Laura Martello-Rooney, PhD: Co-Investigator (0.6 calendar months, 5% effort, Years 1-4)  
Dr. Martello-Rooney, Research Assistant Professor, is the Director of GI Research and oversees the research activities of the Division of Gastroenterology & Hepatology. Dr. Martello-Rooney will oversee all aspects of the Pilot Research Projects on the SUNY Downstate campus.

##### **OTHER DIRECT COSTS**

##### **EQUIPMENT                      \$10,000 (Year 1 only)**

Sub-zero freezer (Year 1 only \$10,000): We are requesting funds for the purchase of a sub-zero freezer to use for the storage of the pancreatic and colon tumor tissues.

##### **SUPPLIES      \$2,000 (Year 1)/\$5,000 (Years 2-4)**

We are requesting funds for tumor collection supplies such as transport medium, PBS, centrifuge tubes, scalpels, accutase and antibiotics; for cell culture supplies such as medium, serum, antibiotics, cell culture dishes/plates, pipets, centrifuge tubes, cryovials, freezing medium, storage boxes, CO2 tanks, liquid nitrogen; for in vitro assay supplies such as antibodies for marker staining, cell proliferation testing, migration/invasion assays, chemosensitivity testing.

##### **OTHER EXPENSES                      \$4,000**

Trainees field work costs (Years 1-4 \$4,000): We are requesting funds to support trainees involved in outreach related to screening, recruitment and retention activities for Pilot project 1 of the grant.

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	Totals (\$)	
Section A, Senior/Key Person		18,879.00
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		18,879.00
Section C, Equipment		10,000.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		33,000.00
1. Materials and Supplies	17,000.00	
2. Publication Costs	0.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	16,000.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		61,879.00
Section H, Indirect Costs		31,905.00
Section I, Total Direct and Indirect Costs (G + H)		93,784.00
Section J, Fee		0.00

## PHS 398 Cover Page Supplement

OMB Number: 0925-0001

## 1. Project Director / Principal Investigator (PD/PI)

Prefix:

First Name\*: Ellen

Middle Name:

Last Name\*: Li

Suffix:

## 2. Human Subjects

Clinical Trial?      ☒ No      ☐ YesAgency-Defined Phase III Clinical Trial?\*      ☐ No      ☐ Yes

## 3. Permission Statement\*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes      ☐ No

## 4. Program Income\*

Is program income anticipated during the periods for which the grant support is requested?      ☐ Yes      ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount (\$)*	Source(s)*
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

## PHS 398 Cover Page Supplement

### 5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?\*      ☒ No      ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: [http://grants.nih.gov/stem\\_cells/registry/current.htm](http://grants.nih.gov/stem_cells/registry/current.htm). Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s):      ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

### 6. Inventions and Patents (For renewal applications only)

Inventions and Patents\*:      ☐ Yes      ☒ No

If the answer is "Yes" then please answer the following:

Previously Reported\*:      ☐ Yes      ☐ No

### 7. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name\*:

Middle Name:

Last Name\*:

Suffix:

☐ Change of Grantee Institution

Name of former institution\*:

## PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	Introduction_Pilot_1_Final.pdf
2. Specific Aims	Aims_Pilot1_Final.pdf
3. Research Strategy*	P20_Pilot_Project_1_ResearchStrategy_Final.pdf
4. Progress Report Publication List	
<b>Human Subjects Sections</b>	
5. Protection of Human Subjects	P1_Protection_of_Human_Subjects_P1.pdf
6. Inclusion of Women and Minorities	IOW_Final.pdf
7. Inclusion of Children	IOC_Final.pdf
<b>Other Research Plan Sections</b>	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	Proj1_LOS.pdf
13. Resource Sharing Plan(s)	Resource_Plan_Proj1031915_eli.pdf
<b>Appendix (if applicable)</b>	
14. Appendix	

## Introduction- Pilot 1 (P1)

We are pleased with this opportunity to respond to the reviewers' comments on our previous application. We were quite pleased that the number of the reviewers evaluated our project as being of high impact. The main concern about the project appeared to be the small number of samples we are proposing to analyze. We are aware that this is a concern if one views the goals of the project as getting statistically significant data concerning genetic variation in tumors from African-Americans versus Caucasians. However, while we do want to do this our overriding goal proposing this project is to get the data of the necessary types and work through the procedures in lab and with analyses so that we can scale up the process. A major objective of the P20 for the Institutional partnering P20 grant is to develop the infrastructure to collect and process URM patient samples in order to generate the data proposed in this P1 project. While we plan to develop an infrastructure for collecting a larger number of samples than will be analyzed in P1, it is important that we provide immediate feedback to the nascent SUNY Downstate GI BioBank on the quality of the data generated from these URM samples. Again, this is a planning grant not an R01 or a P01 grant for instance. And so the goal is to establish the necessary things we need to do to plan for the higher throughput studies. We believe the number of samples we are proposing, as well as types of analyses we are proposing, are ideally suited to this primary goal of this application. We have modified the application to make this more clear. We hope that the new information which includes explanations of why we are proposing to do what we are doing will be considered an appropriate response to the concerns.

We have also made changes in the leadership team. Dr. Jennie Williams, a NIH funded URM investigator, was Research Assistant Professor of Medicine at SUNY Stony Brook at the time of the initial P20 application. She has since been promoted to Associate Professor of Preventive Medicine at SUNY Stony Brook in recognition of her independent research program and has replaced Dr. Li (the overall SUNY contact PI) as the SUNY contact PI for this P1 project.

In addition while this was of course not mentioned by the reviewers the field has changed since we submitted our initial application. We have modified a proposal to include information about targeting new areas within the genome that might be of interest in African American colon cancer samples. We also describe more how we would respond to various contingencies as the field progresses as other ongoing studies among all groups proceed and may require additional funding. Again, we hope that these explanations clarify our overall plan and how we respond to potential new information or changes.

## W. Richard McCombie., PI

### Specific Aims

The incidence and mortality rates from colorectal cancer (CRC) are significantly higher in African Americans (AAs) than for all other racial and ethnic groups in the United States [1-4]. While socioeconomic factors contribute to delayed diagnosis of colon cancer at more advanced stages in AA patients [2-4], there is emerging evidence that AAs, particularly those with high grade tumors, may have poorer outcomes despite receiving equivalent treatment than Caucasians [4]. Identifying molecular differences in AA colon cancers may provide further insights on the biological basis for these differences and may lead to more effective prevention, diagnosis and treatment of AA colon cancer patients [5-12]. The Cancer Genome Atlas (TCGA) Research Network has spearheaded the analysis of human cancers, including human GI tumors, in order to discover molecular aberrations at the DNA, RNA, protein and epigenetic levels, however, representation of underrepresented minorities (URM), including AA in these analyses has been low. For example, the TCGA colon cancer database includes only six samples identified as being collected from African Americans colon out of > 250 samples [13]. Pilot Research Project 1 represents the integration of two separate research projects that are led respectively, **Dr. Jennie Williams** and **Dr. Paula Denoya**, two Stony Brook URM investigators and W. Richard McCombie of CSHL. **Dr. Williams** was investigating alterations in miRNA profiles in African American colorectal cancers. **Dr. Denoya** was working on defining high resolution mapping of altered methylation patterns in clinical samples of colorectal cancers. Both of these investigators had been working in collaboration with Dr. **Dick McCombie** at CSHL, and both were interested in acquiring RNA-Seq datasets using the same Stony Brook GI Biobank colorectal cancer biospecimens. Because of patient demographics, the opportunity to collect AA colorectal cancer biospecimens is low at SUNY Stony Brook, but high at SUNY Downstate. *Thus Pilot Research Project 1 serves to model how the SUNY (Stony Brook and Downstate)-CSHL partnership, coordinates and prioritizes the generation of linked patient based molecular data from biospecimens collected from SUNY Stony Brook and Downstate for multiple investigators. Since the SBU/SDS and CSHL components of this project are so closely integrated, we have included the same text for this pilot project in both applications except for the leadership description. The budgets found in each linked proposal, however, are distinct and do not overlap as explained in the justifications, with the sample collection infrastructure in the SBU/SDS budget and the sequencing and analysis in the CSHL budget.*

**Aim 1 (Overall). Build an integrative partnership between SUNY (Stony Brook and Downstate) and the NCI-designated Cancer Center at Cold Spring Harbor Laboratories to study racial and ethnic differences in colorectal cancer biology using high throughput sequencing methods.**

Sub Aim 1. Build an infrastructure for collecting colorectal cancer biospecimens at SUNY Downstate. This effort will be led by **Dr. Laura Martello-Rooney** who will work closely with **Dr. Ellen Li** who directs the Stony Brook GI Biobank. This process has already been initiated in annotating archived formalin fixed paraffin embedded blocks of colorectal cancer tissues at SUNY Stony Brook and SUNY Downstate to support identifying miRNAs that are differentially expressed in URM led by **Dr. Jennie Williams**. **Dr. Martello-Rooney** will be hiring a research coordinator, a technician and additional equipment and supplies to support prospective collection of colonic resection specimens from Downstate and King's County hospital.

Sub Aim 2. Generate preliminary linked mRNA (RNA-Seq), epigenetic and genetic sequencing datasets at CSHL from RNA and DNAs extracted from URM colorectal tissue and blood specimens collected at SUNY Stony Brook and SUNY Downstate. This effort will be led by **Dr. McCombie**, the Director of the CSHL Sequencing Center. The RNA and DNA libraries will be constructed for Illumina based sequencing. Over 4 years we propose to generate from 40 URM colorectal cancer patients: 1.) linked RNA-Seq mRNA profiles from tumor and adjacent normal mucosal RNA samples; 2.) epigenetic data from tumor and adjacent normal mucosal DNA samples; and 3.) exome data from genomic DNA from peripheral blood mononuclear cells (PBMC) genomic DNA, tumor DNA and adjacent normal mucosal DNA. We anticipate that these linked datasets will prove valuable not only to **Drs. Williams** and **Denoya**, but will also be of great interest to the wider cancer research community.

## Pilot Research Project 1 (P1) Research Strategy

### 1. Significance.

**1A. Colon Cancer Health Disparities.** Colorectal cancer (CRC) is the second leading cause of cancer related deaths in the United States. Multiple studies have reported disparities in the incidence and mortality from CRC among African American patients compared to other racial groups (1). The underlying factors are multiple and include both socioeconomic and biological differences. Socioeconomic factors may contribute to poorer access to health care and delayed diagnosis. On the other hand African American colon cancers tend to be located in the proximal colon (2). The American College of Gastroenterology currently recommends that African Americans begins screening at the age of 45, 5 years earlier than the United States Preventive Task Force recommendations for all average risk individuals at the age of 50 (3).

**Dr. Jennie Williams**, an Associate Professor in the Department of Preventive Medicine at Stony Brook University, is a NIH funded investigator. The role of miRNA in CRC initiation and progression is the core of her research. MicroRNAs are small (17-22 nt) regulatory RNAs that control gene expression via specific sites at the 3'-UTR of their target mRNAs by accelerating mRNA degradation and/or by repression of translation (4). In 2009, Dr. Williams initiated a project to test the hypothesis that differential expression of microRNAs in African American colon cancers could contribute to disparities in colon cancer outcome. This concept was supported by the observation that differential expression of miRNAs in paired colon cancer tumor and adjacent normal colon samples have been previously reported in multiple studies (5). With the acquisition of 15 African American and 15 Caucasian American coded paired tumor/normal formalin fixed paraffin embedded (FFPE) tissue samples linked to coded clinical metadata from the Stony Brook GI BioBank, directed by Dr. Ellen Li, which operates under the umbrella of the Stony Brook Pathology Tissue Bank directed by Dr. Kenneth Shroyer, Chairman of Pathology (see his Letter of Support). **Dr. Williams** detected, via miRNA microarray, upregulation of miR-182 in African American compared to Caucasian American colon cancers. This is noteworthy because independent studies in other patient cohorts and in animal models have linked increased expression of miR-182 with increased risk of developing liver metastases and poorer survival (6).

**1B. Overcoming Barriers to Collecting URM Colon Cancer Specimens Linked to Longitudinal Clinical Metadata.** Most studies involving racial health disparity have included an inadequate number of AA samples, thereby, limiting statistical power to adequately assess important questions concerning risk and prognosis. The patient demographics at Stony Brook University Hospital made it difficult to accrue racially and ethnically diverse CRC samples at a rapid rate. In order to support **Dr. Williams's** RO1 funded research program, efforts were made to develop collaborations with other institutions to acquire additional frozen and/or FFPE tissues from The Cooperative Human Tissue Network, Washington University, Stony Brook University, SUNY Downstate, Kings County Hospital center and Northport Veteran Affairs Medical Center. The collaboration between **Dr. Williams** and faculty members at Washington University was facilitated by **Dr. Ellen Li**, a Professor with joint appointments at SUNY Stony Brook and Washington University St. Louis. The formation of this collaboration was instrumental in Dr. Williams' acquisition of external African American colon cancer samples which were used to confirm her initial miRNA observation. The results from these studies were subsequently published in the *International Journal of Oncology* (5). Unfortunately, clinical data was quite limited, making it impossible for **Dr. Williams** to analyze the contribution of potential confounding co-variables such as diabetes mellitus and obesity, which have been identified as risk factors for colorectal cancer (7). Fortunately, clinical metadata collected by the Stony Brook GI BioBank and the developing SUNY Downstate GI BioBank (directed by **Dr. Laura Martello-Rooney**) over the past year, includes these data points as well as data relating to access to health care, i.e., medical insurance status. Thereby, going forward, **Dr. Williams** will be able to assess the contribution of potential confounding co-variables to CRC development. Thus, this P20 will further our efforts to reduce barriers faced by investigators like **Dr. Williams** in maintaining their research programs on Cancer Health Disparities.

**1C. Mentorship of Trainees and Junior Faculty Investigators interested in Colon Cancer Health Disparities.** **P1** represents the integration of two separate projects presented at the Stony Brook Cancer Center monthly GI Cancer Interest Group, by two Stony Brook URM investigators, **Dr. Paula Denoya** and **Dr. Williams**. **Dr. Paula Denoya** (co-I) is an Assistant Professor in the Department of Surgery and the Division of Colorectal Surgery at Stony Brook University. In 2010, she successfully competed for a Stony Brook School of Medicine Targeted Research Opportunity (TRO) Fusion award to collect epigenetic profiling data in clinical

samples of colorectal cancers. This undertaking was in collaboration with **Dr. McCombie** (contact PI) at CSHL. Their initial plan was to apply a hybrid capture method of mapping the methylation changes, which had been recently developed at CSHL (8) to clinical samples. In order to design the array for the hybrid capture it was necessary to first survey the mRNAs that are expressed in normal colonic mucosa and colon cancers. For this reason a series of microarray followed by RNA-Seq experiments were initiated on HT-29 cells, a cultured cancer cell line, which was treated with and without aza-deoxycytidine, as well as a small set of clinical samples. A comparison of parallel microarray and RNA-Seq data generated from the same samples, resulted in a joint publication between Drs. **Denoya, Williams, McCombie** and **Li** (9). Dr. Denoya in collaboration with Dr. McCombie embarked upon generating RNA-Seq data from Stony Brook GI BioBank colon cancer and adjacent normal colon biospecimens for the purpose of design the hybrid capture array. This data also served to help monitor Q/A for the Stony Brook GI BioBank biospecimen collection protocol. However, as the technology for high resolution mapping of methylation evolved during the course of this project, Dr. McCombie advised Dr. Denoya to use reduced representation bisulfite sequencing (RRBS) for epigenetic profiling of her samples (10).

Because miRNA dysregulation may be linked to alterations in DNA methylation (11) and miRNA in turn regulates mRNA expression (4), **Dr. Williams** became interested in analyzing the potential links between alterations in DNA methylation, miRNA regulation and mRNA regulation. Encouraged by the progress made in generating RNA-Seq and RRBS data from **Dr. Denoya's** samples, **Dr. Williams** began a collaboration with **Dr. McCombie** to generate linked RNA-Seq and RRBS for epigenetic profiles of the same Washington University African American and Caucasian colon cancer nucleic acid samples she had generated her miRNA data on. **Dr. Williams** hopes to test the hypothesis that upregulation of microRNA expression (e.g. miR-182) exerts its effect in the differential incidence of CRC through the downregulation of the putative mRNA targets. In this **P1** project she also hopes to compare differential methylation regions in paired tumor/normal colon samples. Thus far, RNA-Seq data has been generated from 13 tumor/normal paired African American patients and as many samples from Caucasians patients using both the Washington University St. Louis and Stony Brook African American colon cancer specimens. At this point of time, the HT-29 RRBS libraries and 58 RRBS libraries have been generated at CSHL from the Washington University Siteman and Stony Brook GI Biobank paired tumor/normal DNAs including 15 paired African American tumor/normal samples originally obtained from the Siteman Cancer Center. To analyze the RRBS data, Dr. Xuefeng Wang in collaboration with Drs. Williams and McCombie developed a novel algorithm for processing the RRBS data (12).

The patient demographics at SUNY Downstate are much more suitable for collecting valuable URM GI cancer biospecimens. **Dr. Laura Martello-Rooney**, working with the surgeons at Downstate Medical Center and King's County Hospital, estimates that ~50 African American colorectal cancer biospecimens can be collected each year. In contrast, with the Stony Brook BioBank capturing >90% of all patients undergoing resection of colorectal cancer, only 6 African American colon cancer biospecimens have been banked over 3 years. Consequently the major priority for **P1** is to quickly build an infrastructure that will allow **Dr. Martello-Rooney** to collect URM colorectal cancer biospecimens at Downstate Medical Center. In addition to the RNA-Seq and RRBS datasets, **Dr. McCombie** plans to generate linked exome sequencing data on paired colon cancer and adjacent normal colonic mucosa, linked to peripheral blood mononuclear cells (PBMC). These latter datasets are of interest to **Dr. Jennie Williams** who is working on a separate project analyzing the prevalence of P53Pro72Arg polymorphism (SNP:rs1042522) in African American colon cancers (13).

In summary **P1** directly addresses the Cancer Research target areas as stated in PAR-14-152 as follows:

1. This is a "translational" research project that utilizes "emerging technologies in ... genomics".
2. It is designed to "increase biospecimen collection from underserved populations, a critical endeavor to potentially elucidate the biological and genetic factors associated with cancer health disparities."
3. This joint research project will be conducted at the Institutions "serving underserved communities with cancer health disparities." (SUNY Stony Brook and Downstate) with an NCI-designated Cancer center at CSHL) "serving underserved communities with cancer health disparities."
4. It focuses on the general area of "cancer biology" and "molecular epidemiology."
5. The sequencing efforts conducted at the Cancer Center (CSHL) "specifically address areas of cancer disparity."
6. **P1** is aimed at supporting "future grant application submissions for RO1 Awards, projects on P01 and P50 awards or their equivalent."

## **2. Innovation**

The major innovation is to collect and generate linked omic data sets from colorectal cancer patients of African descent in order to boost URM representation of the biospecimens and data. The Cold Spring Harbor Genome Center is home to sophisticated state of the art equipment including Illumina HiSeq 2000 (9), Illumina MiSeq (2), NextSeq 500 (1), Ion Torrent PGM (1) and Pacific Biosciences RS sequencers (2). Between March 2013 and March 2014, the CSHL Genome sequencing core sequenced 2,104 Illumina HiSeq lanes and 144 MiSeq runs, created 1,600 exome and genome sequencing libraries, 85 RNA-Seq libraries and 57 reduced representation bisulfite sequencing libraries. In October 2013 the genome center deployed a new custom LIMS that has greatly improved searching, tracking and reporting abilities, and integrates all information from DNA/RNA sample metadata to sequencing QC data. The database currently holds information on 23,632 Illumina sequencing libraries and 16,537 Illumina sequencing lanes accumulated since 2008. The infrastructure and personnel on site are more than adequate to carry out the proposed sequencing as well as the scale up to a larger project which we plan on applying for additional funding to support with preliminary data obtained under this proposed project.

### **3. Leadership.**

Jennie Williams, Ph.D., contact PI, SUNY Stony Brook. Since the submission of the initial P20 application Dr. Williams has been promoted from Research Assistant Professor of Medicine to Associate Professor of Preventive Medicine with tenure at SUNY Stony Brook. Dr. Williams replaces Dr. Li in the revised P20 application as contact PI for SUNY. Dr. Williams will oversee the bioinformatics and biostatistical analysis of the 'omics data integrated with clinical metadata, in collaboration with Dr. Li

Laura Martello-Rooney, co-I, SUNY Downstate. Dr. Martello Rooney is Research Assistant Professor in the Division of Gastroenterology. Since the initial submission of the P20 proposal in 05/14, she has made tremendous progress in setting up the SUNY Downstate GI Biobank, dealing with the regulatory issues. She has succeeded in transferring URM colon cancer samples from SUNY Downstate to Stony Brook (75 AA FFPE samples with Dr. Li serving as courier to Dr. Williams laboratory).

Paula Denoya, M.D., co-I, SUNY Stony Brook. Dr. Denoya is Assistant Professor of Surgery and played an important role in developing the infrastructure for the SUNY Stony Brook GI Biobank. Dr. Denoya will continue to collaborate with Dr. Williams on the RNA-Seq and RRBS analysis of colorectal cancer specimens.

W. Richard McCombie, Ph.D., contact PI, CSHL Dr. McCombie is a Professor at CSHL and the Director of the CSHL Cancer Center Genomics Shared Resource Sequencing Center at CSHL. He will oversee all the sequencing experiments.

### **4. Approach**

Aim 1 (Overall). Build an integrative partnership between SUNY (Stony Brook and Downstate) and the NCI-designated Cancer Center at Cold Spring Harbor Laboratories to study racial and ethnic differences in colorectal cancer biology using high throughput sequencing methods.

The major goal of this planning grant is to demonstrate the ability of this tri-institutional partnership to increase the collection of biospecimens and generation of high quality integrated 'omics data from URM colorectal cancer patients, particularly those of African descent.

Sub Aim 1. Build an infrastructure for collecting colorectal cancer biospecimens at SUNY Downstate.

Because of the favorable patient demographics at the SUNY Downstate Medical Center, priority will be placed to direct resources to support collection of biospecimens there. **Dr. Laura Martello** will build an infrastructure to support colorectal cancer biospecimen collection at Downstate that will use the same operating protocols used at the Stony Brook and Washington University St. Louis DDRCC Biobank.

Patient recruitment and biospecimen processing in the Stony Brook and Downstate GI BioBank. We anticipate that Dr. **Martello-Rooney** will adopt the same protocol for collecting colorectal cancer biospecimens that is currently in place for the Stony Brook GI Biobank. Currently at the Stony Brook GI Biobank, the research nurse coordinator and the technician monitor the surgical schedule for the Colon Rectal Surgeons at SUNY Stony Brook on the electronic scheduling system and attend the weekly Colon Rectal Surgery Treatment Planning Rounds. After the surgeon ascertains the willingness of the patient to be contacted, the research coordinator consents the patients coming up for resection for longitudinal clinical data, surgical waste tissue, blood and

stool prior to the procedure. Using this approach we have >90% capture of biospecimens at Stony Brook. While we do not anticipate immediately using stool samples we would like to collect these samples to potentially link the molecular findings with alterations in microbiome and diet in the patients (14). Detailed metadata is collected by direct interview of the patient and review of the electronic medical record (emr), including race and ethnicity (self-declared), country of origin, family history of colon cancer or colonic neoplasia, smoking, medications, BMI by the GI Biobank staff. The surgeon notifies the circulating nurse to page down the technician while devascularizing the colonic segment to be removed. The resected specimen is then immediately transported to Surgical Pathology, where a pathologist first ascertains whether the tumor is large enough to collect research material or not. Ex-vivo forceps biopsies are taken using the same forceps used during colonoscopic procedures, to biopsy the affected (tumor region) and adjacent normal appearing mucosa in the ileum and the colon. The forceps biopsies (4-5 biopsies/site) are placed immediately into RNA stabilization solution (15). The specimens are stored overnight at 4 ° C, prior to archiving the samples at -80C. The blood is centrifuged to separate serum (or plasma) from the clot or PMBC). All specimens are assigned a patient code and a sample code and stripped of all identifying information. The IRB approvals are already in place for the Stony Brook Biobank collection process and we anticipate that the IRB approvals will be obtained for the Downstate Biobank collection process prior to the funding start of the planning grant.

#### DNA and RNA extraction of colon tissue biospecimens.

Prioritization of archived coded-deidentified biospecimens collected from URM colorectal cancer patients, particularly those of African descent, at the Stony Brook and Downstate Biobanks will be made for the **Pilot Research Project 1**. Total RNA and DNA will be extracted from the archived biospecimens stored in RNAlater, using the Allprep DNA, RNA and protein kit (Qiagen) to obtain maximal recovery of each analyte.

#### Sub Aim 2. Generate preliminary linked mRNA (RNA-Seq), epigenetic and genetic sequencing datasets at CSHL from RNA and DNAs extracted from URM colorectal tissue and blood specimens collected at SUNY Stony Brook and SUNY Downstate.

State of the art genomic analysis will be conducted on a total of 24 pairs of tumor and adjacent normal mucosal biospecimens collected from URM colorectal cancer patients, preferably those of African descent, at the Cancer Center Genomics Sequencing center at CSHL, which is under the direction of **Dr. McCombie**. We are aware that the number of samples that we will be handling is small and unlikely to yield statistically significant results. On the other hand, we should note that in the first year we will match the data available in the Cancer Genome Atlas for colon cancer in African Americans. Being aware of this limitation, our goal is to establish the feasibility of this tri-institution partnership to obtain the samples, extract the DNA and RNA from the samples, carry out quality control on them and then perform state of the art genomic analysis on each tumor normal pair of samples. The state of the art analysis we will do will be comprised of RNA sequencing, RRBS analysis and exome sequencing. Together these analyses will tell us about differences in gene expression between the tumor cells and normal cells, methylation differences between the tumor cells and normal cells and coding variants in the genome of the tumor cells versus the normal cells from a given colorectal cancer patient. It will also allow us to carry out rigorous quality control on both RNA and DNA obtained from Stony Brook and Downstate, and optimize sample transfer from those institutions to CSHL allow us to set up access for SUNY to the CSHL Genome Center LIMS and provide feedback on sample quality and sample tracking to optimize the entire pipeline. Finally it may even provide us preliminary insights on molecular differences between colon cancers in patients of African descent compared to those of European or Caucasian descent. We're cognizant that the field of cancer genomics is very rapidly evolving. We selected to do these set of data for a number of reasons fitting as much if not more so with the pilot/planning nature of this application than about the goals of the studies from a genomics standpoint.. Ideally, we would do the analyses we are proposing, exome, methylation, and transcriptome, and also include whole genome sequencing. This of course would be considerably more expensive than what we are proposing and hence we would only be to do a very small number of samples. The idea behind what we are proposing is to allow us to set up the infrastructure for sample and data transfer among the sites. This includes transferring the actual samples, access by Stony Brook personnel to the CSHL laboratory information management system and feedback on various aspects of the sample nucleic acids. If, for instance, we were to just do genome sequencing we would not get good feedback on the transcriptome information and RNA quality. By doing the set we are proposing will get information both on DNA and RNA and experience in handling them; troubleshooting if necessary and providing feedback on sample quality and quantity. We should also note that in our very considerable experience it is easier to prepare whole genome libraries than it is to prepare exome capture libraries. Hence, developing the ability to do exome capture from these samples will by necessity give us the ability to do

genome sequencing at a subsequent time if we decide to do so. In addition by providing the multiple data sets it will provide multiple components of data that the downstream analytical people would be able to use to analyze and develop tools to integrate multiple data sets; again something that would be missing if we just did whole genome sequencing. Since our initial application the field has changed somewhat. There have been two publications on exome sequencing from colon cancer samples from African-Americans (16, 17). It appears that neither of these does extensive comparison of methylation RNA and exome sequencing. They did however identify candidate genes that might be associated with African-American cancer specifically. In addition to these studies there have been studies published on the nucleotide repeat expansion and microsatellite stability (EMAST) (18). These might be linked to EMAST gene instability or loss of function. We will make sure that our arrays for capturing include the genes identified in these papers. We will also work to have a specific capturing of regions affected by the EMAST so that we can evaluate them in the patient samples as well. Since we developed exome capture in (19), we have been extremely active in pushing the field forward. We do a number of projects some of them involving thousands of exomes using targeted exome like captures which we typically call exome plus which include as standard exome capture that is commercially available plus enhanced targets. We will apply this strategy to the proposed project now that we have targets which to access.

*RNA Seq Analysis.* Coded de-identified paired tumor and normal RNA samples from 24 URM colorectal patients, with RIN scores  $\geq 7$  will be submitted to the CSHL Genome Sequencing Center from the Stony Brook and/or Downstate GI Biobanks. RNA-Seq libraries will be prepared and sequenced at Cold Spring Harbor Laboratories using the TruSeq mRNA Sample Preparation Kit (Illumina Inc., San Diego, CA). mRNA will be purified and fragmented from total RNA (100ng), followed by cDNA synthesis with random hexamers. This cDNA will then undergo end repair, adapter ligation, and size selection using AMPure XP beads (Beckman Coulter Inc., Brea, CA). The cDNA will be PCR amplified. Six libraries will be pooled together to create a composite library. This composite library will be sequenced on 1 lane of the flow cell of a using Illumina HiSeq 2000 sequencer (Illumina Inc., San Diego, CA) in a paired end 100bp run, such that an average of 66 million reads will be obtained per biological sample. The sequence files (via FTP transfer) as well as QC tables, intensities plots and base quality graphs for each lane of sequencing will then be made available to Stony Brook and Downstate for further analysis. Drs. Denoya, Williams, McCombie and Li (9), have published some of the RNA-Seq data generated at CSHL from Stony Brook RNA samples, comparing various differential gene expression algorithms.

*Reduced Representation Bisulfite (RRBS) sequencing* Coded de-identified paired tumor and normal DNA samples from the same URM colorectal patients will be submitted to the CSHL Genome sequencing center will be prepared according to the protocol published by (10). Briefly, An MSP1 digestion will be performed, and methylated Illumina adapters will be ligated to the DNA fragments. After ligation, twelve libraries will be pooled together. A ligation test will be performed. If the test is successful, the pooled library will be treated twice with bisulfite using the Qiagen EpiTect kit. A test PCR will be performed with a variable number of amplification cycles to determine the optimum PCR conditions for each pooled library. A full scale PCR will then be performed. Each pooled library will be sequenced in one lane of a HiSeq single read 76bp flow cell. As discussed above, 57 RRBS libraries constructed by samples submitted by Drs. Williams and Denoya are in the process of being sequenced at CSHL. The sequence files (via FTP transfer) as well as QC tables, intensities plots and base quality graphs for each lane of sequencing will then be made available to Stony Brook and Downstate for further analysis. The RRBS data will be pre-processed using the MethyQA pipeline (15), which starts from fastqc quality check to trim, alignment referring to hg19 and methylation rates calculation. All parameters will be set as default, except that [-f <string>] FASTQ format will be set as "sanger". After trimming, BRAT will be utilized as a default alignment tool. After alignment, the pipeline will generate the methylation ratio file using the ACGT-count function of the BRAT package. It will then generate summary tables and plots histograms for the statistical summary of all target regions. If the cytosine in the non CG regions have very high bisulfite-conversion rates (i.e.,  $> 0.999$ ) as shown in the summary tables and plots, we will continue with further downstream analysis. The sequence alignment will be done again using Bismark, and methylated C counted for each CpG using DMAP (20). The Fisher exact test will be used to identify differentially methylated regions after filtering for coverage.

*Exome sequencing.* Exome sequencing was developed at CSHL and we are very adept at it (21). We currently use a Nimblegen solution capture approach for exome sequencing. Samples will be subjected to capture and

sequencing based on established methods (21-23). We typically use 6 barcoded samples per lane, for germline DNA on a HiSeq 2000 instrument. However, due to expected heterogeneity of the tumor samples we will evaluate higher coverage. We currently use HiSeq 2000 instruments but we might upgrade to the newer HiSeq 2500 instrument prior to when this project would be initiated. If we do this we would be able to achieve the desired target coverage with somewhat more samples per lane. This will be determined empirically. Image processing and basecalling will be performed as the runs progress with Illumina's Real Time Analysis (RTA) software. The binary basecall files will be streamed to a shared Linux server. The Illumina Casava pipeline will be used to convert the binary files to fastq files and to demultiplex reads into individual files for each barcode, allowing 1 mismatch in each barcode sequence. Reads will be aligned to the human reference assembly (UCSC hg19 - <http://genome.ucsc.edu/>) using the BWA aligner (24) allowing 2 mismatches in the 30-base seed. Alignments will be paired with BWA, then imported to binary (bam) format, sorted and indexed using SAMtools (25). Picard (<http://picard.sourceforge.net/>) will be used to remove PCR duplicates. Bamtools (26) will be used to filter alignments to retain only properly paired reads (reads aligned with appropriate insert size and orientation), and to select alignments with a minimum mapping quality score of 20. Target coverage for each amplicon will be assessed using Picard's HSmetrics utility, and both depth and breadth of coverage will be reviewed for each sample. Only samples which reach a depth of at least 20X over  $\geq 80\%$  of the targets will be included in the downstream analysis. The Genome Analysis Toolkit (27) will be used to generate SNP and small indel calls for the data within the targeted regions. Local read realignment around indels and base quality score recalibration will be done with GATK. Initially GATK Unified Genotyper and/or Haplotype Caller will be used for SNP/Indel calling. Variants will be recalibrated using the GATK variant quality score recalibration protocol. Joint variant calling and genotyping of tumor/normal samples will be performed in order to achieve a high quality, accurate call set. However, as the GATK caller is more tuned to germline variation and may miss some low frequency variants, we will test several somatic variant callers (such as MuTect (28), and VarScan (29)) to determine which will provide the best sensitivity for samples with a low tumor fraction while maintaining the lowest false positive rate on our data.

## **5. Project Evaluation.**

Updates on URM colorectal cancer biospecimen collection and generation of linked RNA-Seq, RRBS and exome sequencing will be reviewed quarterly by the Steering Committee during one of the monthly GI Interest group meeting. We will track the availability of URM biospecimen collection and the quality of the extracted RNA and DNA, the samples that have been submitted for library construction to CSHL, which libraries have been completed, and which libraries have been sequenced.

We also want to point out that we are aware that between the time this revised P20 grant application is submitted and the time it is potentially funded, the cancer genetics field will continue to evolve as will the situation in our respective institutions. One potential change might be that Dr. **Williams** is submitting an R01 grant to carry out a substantial number of RNA-Seq and RBBS sequencing on samples from underrepresented minorities. Both Dr. **McCombie** and Dr. **Martello-Rooney** are associated with Dr. **Williams'** R01 grant application. If her R01 grant were to be funded this would clearly put us in a different situation in terms of this P20 proposal at least to some degree. Again the purpose of this pilot/ planning P20 grant is not so much to do a large number of samples but rather to put everything in place so that it can be scaled up. Depending on what might be funded from Dr. **Williams'** R01 grant and if this P20 planning grant were funded as well, we would likely drop the RNA-Seq and RBBS from the P20 P1, expand exome sequencing, and add some form of whole genome sequencing into the mix of the overall program. At CSHL my group is particularly interested in the impact of long read length whole genome sequencing in understanding cancer. We are currently working, under separate funding, in carrying out high coverage sequencing of the SKBR3 breast-cancer cell line using very long read sequencing (read lengths in excess of 10,000 bases) to carry out analysis of this cancer genome. Preliminary data indicates that such things as rearrangement breakpoints and indels are likely to be seen at far higher resolution with the long read chemistry than the standard Illumina chemistry (W. R. McCombie, Michael Schatz, John McPherson, et al. unpublished). Right now this is a relatively expensive way of doing whole genome sequencing but the cost is dropping rapidly and is likely to drop considerably by the time that this current application might receive support. These are some of the ideas of how we might modify the proposal depending on other funding and the way that cancer genomics has evolved by the time we would begin the program if funding were awarded. We believe we have considerable expertise in this area and have published a whole genome cancer analysis studies (30) and our main mission with this application would be funded with this pilot project is to put in place all the steps necessary for a fully functioning, large-scale cancer genomics initiative to study underrepresented minority colon cancer cases.

## Pilot Research Project 1 (P1) – Protection of Human Subjects

### 1. Risks to Human Subjects

#### 1A . Human Subjects Involvement, Characteristics, and Design

The overarching goal of pilot research project **P1** is to obtain preliminary colonic genomic and epigenomic data comparing between URM and non-URM colon cancer patients. . The **P1** budget will be directed to recruitment of 240 URM (African-American) patients (60/year) at SUNY Downstate as Dr. Martello-Rooney works with Dr. Vignesh and Salifu to develop the SUNY Downstate BioBank. While SUNY Stony Brook site (Dr. Williams and Dr. Denoya working with Dr. Li) will be recruiting predominantly non-URM (Caucasian) patients for the SUNY Stony Brook Biobank, the support for this effort will be obtained from other funding sources using the identical protocol detailed below. For this reason the non-URM colon cancer patients will not be included in the P20 **P1** enrollment table. While downstream nucleic acid products will be transferred to CSHL for analysis, no one from CSHL will have access to link the SUNY Downstate (or SUNY Stony Brook) samples and data back to the patient. Similarly no one from SUNY Stony Brook will be able to link the SUNY Downstate patient samples and data back to SUNY Downstate patients, and conversely no one from SUNY Downstate will be able to link SUNY Stony Brook patient samples and data back to SUNY Stony Brook patients. Dr. Williams at SUNY Stony Brook will be provided with coded clinical metadata stripped of identifying information from SUNY Downstate and will not be able to link these samples back to any of the patients.

The patients included in the study are those undergoing surgical resection of colon cancer for clinical indications. The patients typically present between after the age of 50 with African Americans possibly presenting earlier by five years (90%). Seventy to 90% of the patients at SUNY Downstate and Kings County Hospital are African American. The combined surgical volume for these resections at SUNY Downstate and Kings County Hospital is ~80/year. Please note that as we build the SUNY Downstate GI Biobank, we will be collecting more samples than the number that will be analyzed in **P1**.

The SUNY Downstate GI BioBank (led by Dr. Martello-Rooney) works closely with the surgeons at SUNY Downstate and Kings County Hospital surgeons to identify all patients being scheduled for colectomy. The surgeons carrying out the procedure (for clinical care) will ask the patient at the time of scheduling the procedure whether the patient is willing to be approached for donation of biospecimens. If the patient is willing the consent forms will be provided in the clinic or mailed to the patient for review ahead of the procedure or surgery. The consents specifically address whether the patient is willing to consent to genetic work, generation of cell lines, access to surgical waste, collection of blood tubes (EDTA blood for PMBC DNA), and collection of longitudinal clinical data.

#### 1B Sources of Materials

1B1 Surgical waste samples from surgical resection of PDA. Dr. **Martello-Rooney** has established close collaborative relationships with surgeons at SUNY Downstate and the King's County Hospital in recruiting all patients undergoing surgical resection of pancreatic tumors for the SUNY Downstate GI BioBank. Dr. Martello Rooney will oversee the collection of longitudinal clinical data, blood, stool and surgical waste from these patients. Dr. Martello-Rooney will oversee the rapid transport of the freshly resected colon cancer tissue to Surgical Pathology so that the attending surgical pathologist can supervise the collection of the research samples from the surgical waste, after insuring that adequate tissue is obtained for clinical diagnostic purposes. Dr. Martello-Rooney will oversee collection of the tumor and adjacent normal colonic mucosa following the same standard operating procedures currently used by the SUNY Stony Brook and Washington University St. Louis GI BioBanks. These coded samples, stripped of identifying information, will be distributed not only to **Dr. Williams** for carrying out the proposed **P1** project, but we anticipate will be distributed to other SUNY Downstate, SUNY Stony Brook and CSHL investigators. While the prioritization and distribution of SUNY Downstate BioBank samples will be determined locally by that institution, we anticipate that their policy will be similar to the one currently implemented at SUNY Stony Brook GI BioBank. Investigators requesting tissue will submit a formal application briefly describing their project and providing a copy of IRB approval. For the SUNY Stony Brook GI BioBank, priority is given to collaborative projects that include SUNY Stony Brook basic investigators and clinicians as co-investigators.

1B2 Collection of EDTA blood tubes. The blood tubes will be drawn from the patient either during the insertion of the intravenous line for the procedure/surgery, or prior to the patient being awakened from sedation. The tube will be processed immediately using standard operating procedures within the GI BioBank to separate the

plasma from the cellular material. The plasma will be aliquoted and archived within the GI BioBank at -80°C. The PMBC will be processed for isolation of genomic DNA using GI BioBank standard operating procedures. The blood samples and their downstream products will be stripped of all identifying information and assigned a patient code, encounter code and sample ID so as to link the blood samples with the tissue samples and the clinical data.

1B3 Collection of longitudinal clinical data If the subject consents to participate in the research database, their participation in the database will be indefinite. If informed consent for a research database is obtained, the SUNY Downstate BioBank staff will review the existing electronic medical records for defined endpoints change in medications (e.g. chemotherapy) and defined clinical endpoints (local recurrence, metastases). If this information is not available by review of the electronic medical records, the subjects have given permission for the BioBank physician staff to contact the patient directly to obtain the information on a yearly basis. Clinical information will be collected using the same data elements and controlled vocabulary used at SUNY Stony Brook. The data elements will include gender, race age at encounter, phenotype (e.g. colon cancer), cancer stage, smoking, alcohol, diabetes, BMI, health insurance status. The clinical data will be stripped of all identifying information and assigned a patient code, encounter code so as to link this data with the samples and their downstream products and data generated from the samples.

1B4. Collection of preoperative stool samples. If the subject consents to participate, the patient will be given a food diary identical to the one currently used by the SUNY Stony Brook GI BioBank (Dr. Jennie Williams). Collection of preoperative stool samples the day prior to surgery will follow standard operating protocols currently used by the SUNY Stony Brook and Washington University St. Louis GI Biobanks. While these samples will not be analyzed in the proposed P1 project we anticipate that in the near future investigators will be interested in generating gut microbiome data (16S rRNA, shot gun DNA, bacterial metatranscriptomics and bacterial metabolomics) and linking that data to the type of human 'omics data generated by the **P1** project.

## **1C. Potential Risks**

1C2 Surgical waste samples from surgical resection of PDA. There are significant complications associated with pancreatic surgery directed at removing PDA. However, because the patients are already scheduled for the surgical operation for clinical care there is no additional risk to the patient associated with donating surgical waste from the operation for research purposes. There is a very small risk that identifying information may be released.

1C3 Collection of EDTA blood tubes. The risks of blood drawing include 1.) discomfort at the site of needle insertion (likely); 2.) bruising, bleeding at site of needle insertion. Dizziness or faintness at the time of blood removal (less likely). There is a rare risk of infection as a potential risk of blood drawing. . There is a very small risk that identifying information may be released.

1C3 Collection of longitudinal clinical data. . There is a very small risk that identifying information may be released.

1C4. Collection of preoperative stool samples. There is a very small risk that identifying information may be released.

## **2 Adequacy of Protection Against Risks**

### **2A Recruitment and Informed Consent**

The SUNY Downstate GI BioBank (directed by Dr. Martello-Rooney) will follow the same procedures currently in place for the Stony Brook GI Biobank (directed by Dr. Li) .Dr. Rooney will work closely with SUNY Downstate and King's County Hospital surgeons to identify all patients being scheduled for resection of colon cancer. The surgeon carrying out the procedure (for clinical care) will ask the patient at the time of scheduling the procedure whether the patient is willing to be approached for donation of biospecimens. If the patient is willing the consent forms will be provided in the clinic or mailed to the patient for review ahead of the surgery. The consents specifically address whether the patient is willing to consent to genetic work, generation of cell

lines, EUS-FNB research biopsies or access to surgical waste for resection of colon cancer, collection of blood tubes (EDTA blood for PMBC DNA), collection of stool and collection of longitudinal clinical data. If the patient decides to participate in contributing collection of surgical waste, blood, stool, longitudinal clinical database, the patient will sign the standard GI BioBank consent form in the presence of Dr. Martello-Rooney or her designee. Dr. Martello and her staff have been trained in good clinical practices and are highly experienced in providing and obtaining informed consent in this patient population.

The patient samples and clinical data will be stripped of identifiers and assigned a patient code, encounter number, and sample ID. Initially samples will be transported to the SUNY Stony Brook GI BioBank for further processing to extract downstream products (e.g. nucleic acids), however the overall goal is to develop the SUNY Downstate GI BioBank so that it can immediately process the samples to generate the downstream products. Furthermore no one from CSHL will have access to link the SUNY Downstate (or SUNY Stony Brook) samples and data back to the patient. Similarly no one from SUNY Stony Brook will be able to link the SUNY Downstate patient samples and data back to SUNY Downstate patients, and conversely no one from SUNY Downstate will be able to link SUNY Stony Brook patient samples and data back to SUNY Stony Brook patients.

## **2B. Protections Against Risk**

Because the patients are already scheduled for the surgical procedures there is no additional risk to the patient for collection of the samples other than the minimal risk of blood drawing. To minimize the risk of drawing research samples we will try to coordinate the collection of research samples with the collection of blood samples for clinical care. The patient codes are kept on a separate database with the appropriate electronic fire-wall protections to prevent breach of privacy. Access to this file will be limited to Drs. Martello-Rooney and Dr. Li and a limited number of designees on the GI BioBank staff.

## **3 Potential Benefits of the Proposed Research to Human Subjects and Others**

There is no direct benefit to the human subjects. Their donations will help investigators using the Biobanks improve treatment, diagnosis and understanding of GI cancers. Conducting research on these samples, including the research proposed in this application may create new tests, treatments or cures. If it does, the patients who have donated samples to the Biobanks will not receive any money from those products. In summary, we believe that the risks of participating are very small for the patients and the potential benefit for improving diagnosis and treatment of GI cancers is great.

## **4 Importance of the Knowledge to be Gained**

African Americans are at risk for a higher incidence and increased mortality from colon cancer.

## **Inclusion of Women and Minorities**

We will make every effort to include samples from women in this study. Because of the patient demographics at SUNY Downstate and King's Hospital and the study design, the subjects enrolled for this study will be minority.

## Planned Enrollment Report

**Study Title:** Pilot 1: Genomic and epigenomic profiling of colon cancers in racial and ethnic minority patients

**Domestic/Foreign:** Domestic

**Comments:**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	120	120	0	0	240
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	120	120	0	0	240

Study 1 of 1

## **Inclusion of Children**

Children are not included in the study group. These cancers are extremely rare in children and we do not expect to see them.

## Pilot Research Project 1 (P1) – References

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March 12, 2015

Dear Dr. Li:

I am extremely happy to serve as a Co-Investigator on this proposal submitted in response to the Department of Health and Human Services P20 research project titled "*Feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research*". I am indeed very excited about collaborating with investigators at SUNY Downstate and Cold Spring Harbor Laboratory. My research interests lie in biomarker discover using novel miRNA for noninvasive detection of colon cancers in African, Caucasian and Hispanic Americans. In addition, I am generating colon cancer cell lines of African and Hispanic American descent to assess differential response of racial and ethnic groups to chemotherapeutic/-preventive agents. As such, I am presently collaborating with SUNY Downstate and Cold Spring Harbor Laboratory for the acquisition of prospective tissue and sample analysis, respectively. This work is supported by a NIH R01 of which I am now submitting a renewal.

I presently serve as Co-PI for NIH's Minority Access to Research Careers (MARC) and a Bridges to Baccalaureate Program for minority students. I am submitting the MARC grant for renewal and, upon renewal, will serve in the role as PI. The goals of the MARC and bridges programs are to increase nationally the number of PhD scientists from underrepresented minority groups engaged in biomedical research. These opportunities are offered to undergraduate students at SBU and Long Island community colleges. In addition, I have served as a faculty mentor for a number of minority undergraduates and high school students. These endeavors are in line with the Aims and goals of your proposal. If awarded, I look forward to providing my expertise to your collaborative partnerships.

Sincerely,

A handwritten signature in black ink, appearing to read "Jennie L. Williams".

Jennie L. Williams, PhD  
Associate Professor  
Department of Preventive Medicine  
Department of Medicine  
Division of Cancer Prevention



March 16, 2015

To whom it may concern:

This letter confirms my willingness to serve as a co-investigator in this project to build an integrative partnership between two SUNY medical campuses, Stony Brook and Downstate, and the NCI-designated Cancer Center at Cold Spring Harbor Laboratories to study racial and ethnic differences in colorectal cancer biology using high throughput sequencing methods.

As an academic colorectal surgeon, I have made a strong commitment to conducting clinical translational research in colorectal cancer. I was the PI of an institutional seed award in launching a collaborative project between Stony Brook University and Cold Spring Harbor Laboratories (Drs. Antoniou and McCombie) in linking high resolution methylation mapping to mRNA (RNA-Seq expression profiling). I am the senior author of a manuscript reporting our initial expression profiling experiments using a cultured colon cancer cell line. I am delighted at continuing this project now with a focus on examining racial and ethnic differences in colorectal cancer biology in collaboration with the other members of this investigative team. I and other members of the colorectal surgery division have worked closely with Dr. Li to expedite the prospective banking of all colorectal surgical resections performed in my division and to assist in the longitudinal tracking of the patients we have recruited to donate their tissues and clinical information. I have been an active participant of the Stony Brook Cancer Center GI interest group since its inception in July 2012.

In addition I have a personal interest in reducing racial and ethnic disparities in colorectal cancer outcomes and in training underrepresented minority students in cancer research. I look forward to participating in the educational workshops, sponsored by the Training and Education Core, aimed at introducing doctoral students (M.D.-Ph.D. and Ph.D) to the clinical side of colorectal cancer.

Sincerely,

A handwritten signature in black ink, appearing to read "Paula Denoya".

Paula Denoya MD  
Assistant Professor of Medicine  
Department of Surgery, Division of Colorectal Surgery  
Stony Brook University Hospital

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SUNY  
**DOWNSTATE**  
Medical Center

University Hospital of Brooklyn  
College of Medicine  
School of Graduate Studies  
College of Nursing  
College of Health Related Professions

Department of Medicine  
Division of Gastroenterology & Hepatology

March 11, 2015

Ellen Li, MD, PhD  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

Dear Dr. Li:

This letter confirms my commitment as a Co-Investigator for the study entitled "Feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research" proposed in this application and submitted in response to the NIH/NCI P20 Funding Opportunity for "Feasibility Studies to Build Collaborative Partnerships in Cancer Research". My involvement relates to oversight of the Pilot Projects at the SUNY Downstate campus in addition to the training of students. As PI of the SUNY Downstate IRB for miRNA analysis of colon cancer samples, I have been coordinating with the Department of Pathology the retrieval and transfer of colon tumor fixed tissue sections to SUNY Stony Brook for testing and this will be extended to colon tumor fresh tissues for the development of colon cancer cell lines. I also have been working closely with Drs. Vignesh and Grossman, in the GI Division, who will be providing fine-needle biopsy pancreatic tumor specimens from African American patients for the generation of pancreatic organoids.

As Director of GI Research, I have been involved in the initiation of various translational research projects focused on pancreatic cancer. These projects have included as participants GI Fellows, Internal Medicine Residents as well as Medical and Graduate students. I welcome the opportunity to expand the project opportunities as a continued way to expose them to the value of research especially as it relates to cancer health disparities.

Sincerely,

A handwritten signature in cursive script that reads "Laura Martello-Rooney".

Laura Martello-Rooney, PhD  
Director of GI Research  
Research Assistant Professor of Medicine  
Division of Gastroenterology & Hepatology  
SUNY Downstate Medical Center  
450 Clarkson Ave, MSC 1196

**State University of New York Downstate Medical Center**

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[laura.martello-rooney@downstate.edu](mailto:laura.martello-rooney@downstate.edu)

## Resource Sharing Plan: Pilot 1

We will follow relevant NIH guidelines for data sharing, in accordance with NIH Resource Sharing Policy and the NIH Genomic Data Sharing Policy effective January 25, 2015, the investigators will share data and resources at the earliest opportunities throughout this research, subject to patient privacy concerns. Following careful curation of sequence data and clinical metadata, the SteeringCommittee will review the release of those coded and deidentified data to the appropriate NCBI databases (dbGAP,Short Read Archive or SRA) using a code that is different from the code used internally. Tables on cohort subject and sample metadata will be deposited in dbGAP, which is a controlled access database. We anticipate that the data generated by the team will be made available as somatic variant data and can therefore be placed on publicly accessible repositories. In addition, results will be written up and sent for publication in relevant journals and the investigators will seek to present publishable results at scientific conferences worldwide.

## APPLICATION FOR FEDERAL ASSISTANCE

**SF 424 (R&R)****5. APPLICANT INFORMATION****Organizational DUNS\*:** 8048782470000

Legal Name\*: The Research Foundation for SUNY, Stony Brook University  
 Department: Office of Sponsored Programs  
 Division: OVPR  
 Street1\*: STONY BROOK UNIVERSITY  
 Street2: The Office of Sponsored Programs  
 City\*: STONY BROOK  
 County:  
 State\*: NY: New York  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 117940000

Person to be contacted on matters involving this application

Prefix: First Name\*: Middle Name: Last Name\*: Suffix:  
 Ms. Andria Adler  
 Position/Title: Grant Administrator  
 Street1\*: W5510 Melville Library  
 Street2: Stony Brook University  
 City\*: Stony Brook  
 County: Suffolk  
 State\*: NY: New York  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 117943362  
 Phone Number\*: 631 632-1610 Fax Number: 631 632-6963 Email: andria.adler@stonybrook.edu

**7. TYPE OF APPLICANT\***

X: Other (specify)

Other (Specify): Non Profit

**Small Business Organization Type**☐ Women Owned☐ Socially and Economically Disadvantaged**11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT\***

Pilot Project Research Project 2

**12. PROPOSED PROJECT**

Start Date\* Ending Date\*  
 09/01/2015 08/31/2019

**Project/Performance Site Location(s)****Project/Performance Site Primary Location**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY, Stony Brook University  
Duns Number: 8048782470000  
Street1\*: STONY BROOK UNIVERSITY  
Street2: The Office of Sponsered Programs  
City\*: STONY BROOK  
County: Suffolk  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 117940000  
Project/Performance Site Congressional District\*: NY-001

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**Project/Performance Site Location 1**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY, Downstate Medical Center  
DUNS Number: 0407963280000  
Street1\*: 450 Clarkson Avenue  
Street2:  
City\*: Brooklyn  
County:  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 112030000  
Project/Performance Site Congressional District\*: NY-009

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File Name

**Additional Location(s)**

## RESEARCH &amp; RELATED Other Project Information

<b>1. Are Human Subjects Involved?*</b> <input checked="" type="radio"/> <b>Yes</b> <input type="radio"/> <b>No</b>	
1.a. If YES to Human Subjects	
Is the Project Exempt from Federal regulations? <input type="radio"/> <b>Yes</b> <input checked="" type="radio"/> <b>No</b>	
If YES, check appropriate exemption number:    — 1 — 2 — 3 — 4 — 5 — 6	
If NO, is the IRB review Pending? <input type="radio"/> <b>Yes</b> <input type="radio"/> <b>No</b>	
IRB Approval Date:	
Human Subject Assurance Number	
<b>2. Are Vertebrate Animals Used?*</b> <input checked="" type="radio"/> <b>Yes</b> <input type="radio"/> <b>No</b>	
2.a. If YES to Vertebrate Animals	
Is the IACUC review Pending? <input type="radio"/> <b>Yes</b> <input type="radio"/> <b>No</b>	
IACUC Approval Date:	
Animal Welfare Assurance Number	
<b>3. Is proprietary/privileged information included in the application?*</b> <input type="radio"/> <b>Yes</b> <input checked="" type="radio"/> <b>No</b>	
<b>4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*</b> <input type="radio"/> <b>Yes</b> <input checked="" type="radio"/> <b>No</b>	
4.b. If yes, please explain:	
4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? <input type="radio"/> <b>Yes</b> <input type="radio"/> <b>No</b>	
4.d. If yes, please explain:	
<b>5. Is the research performance site designated, or eligible to be designated, as a historic place?*</b> <input type="radio"/> <b>Yes</b> <input checked="" type="radio"/> <b>No</b>	
5.a. If yes, please explain:	
<b>6. Does this project involve activities outside the United States or partnership with international collaborators?*</b> <input type="radio"/> <b>Yes</b> <input checked="" type="radio"/> <b>No</b>	
6.a. If yes, identify countries:	
6.b. Optional Explanation:	
<b>7. Project Summary/Abstract*</b>	Filename P2_Summary_Final.pdf
<b>8. Project Narrative*</b>	P2_Narrative_Final.pdf
<b>9. Bibliography &amp; References Cited</b>	Pilot_Research_Project_2_References_Final.pdf
<b>10. Facilities &amp; Other Resources</b>	
<b>11. Equipment</b>	

## Summary

Pancreatic cancer holds the worst survival rate of the common malignancies, in part due to the poor response to treatments. The clinical options available to pancreatic cancer (PDA) patients are determined by the extent of disease progression, and unfortunately the vast majority of patients are ineligible for curative surgical approaches. African Americans and other underrepresented minorities have a higher incidence of, and mortality from, pancreatic cancer. In particular, African Americans have a relative risk of 1.7 for men and 1.5 for women. While Hispanic Americans do not exhibit the same level of elevated risk as African Americans, both populations are at higher risk for diabetes and obesity, two conditions associated with elevated risk for pancreatic cancer. Accordingly, our proposed work will first address the genetic and epigenetic differences that influence pancreatic cancer incidence and mortality in African American, Hispanic American, and Non-Hispanic White American patients. We hypothesize that in addition to the increased incidence of KRAS<sup>G12V</sup> driver mutations observed in the African American population, there are other genetic and epigenetic differences that underlie the heightened malignancy of this disease in specific racial populations. These alterations may also influence other disease states that are associated with increased pancreatic cancer risk, such as diabetes, obesity, and chronic pancreatitis. Understanding these differences may identify new diagnostic and therapeutic targets that are more efficient at detecting and treating pancreatic cancer in these at-risk populations.

To accomplish these goals, we will use a new three-dimensional, cell culture model system of pancreatic cancer progression called organoids. This culture system facilitates the rapid isolation and establishment of organoid lines from both normal and malignant human tissue. Upon isolation of patient-derived organoids from biopsies (fine needle aspirates), we will compare their genomes and transcriptomes both between racial and ethnic populations. Understanding the genetic and epigenetic counterpart to pancreatic carcinogenesis in tractable model systems will directly lead to the discovery of new biomarkers of pancreatic cancer such that early detection strategies can be developed. In addition, our findings may inform different treatment strategies and targets depending on the genomic and epigenomic landscape of the different patient populations. Given that these organoids are amenable to genetic manipulation through viral transduction or CRISPR/Cas mediated gene editing, these studies will enable iterative cycles of discovery and validation for future studies of genetic and epigenetic drivers of pancreatic cancer in under represented minorities.

**Narrative**

We will employ a feasibility study to culture pancreatic organoids obtained from endoscopic ultrasound guided biopsies of URM patients following a new diagnosis of pancreatic ductal adenocarcinoma (PDA). To accomplish this, ten URM patient samples will be cultured per year for four years. These organoids will be used to establish the genetic and gene expression landscape of this malignancy. We will characterize these human-derived cultures with genomic and transcriptomic analyses in collaboration with the McCombie laboratory. In addition, we will evaluate the cellular features of URM pancreatic cancer by performing tumor progression analyses on orthotopically transplanted organoids. Finally, the molecular and cellular information obtained by our laboratories will be correlated to the clinical outcome and ethnicity of the patients.

## RESEARCH &amp; RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator				
Prefix:	First Name*: Ellen	Middle Name	Last Name*: Li	Suffix:
Position/Title*:	Chief			
Organization Name*:	The Research Foundation for SUNY, Stony Brook University			
Department:	Medicine			
Division:	Gastroenterology Hepatology			
Street1*:	101 Nicolls Road Heath Science Center			
Street2:	T-17 Room 060			
City*:	Stony Brook			
County:	Suffolk			
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117948173			
Phone Number*:	631-444-2119	Fax Number:	631-444-8886	E-Mail*: ellen.li@stonybrook.edu
Credential, e.g., agency login: ELLENLI1				
Project Role*: Other (Specify)		Other Project Role Category: Project Lead		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:				
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Juan Carlos	Middle Name	Last Name*: Bucobo	Suffix:
Position/Title*:	Assistant Professor of Medicine,Dir Endoscopy			
Organization Name*:	The Research Foundation for SUNY, Stony Brook University			
Department:	Medicine			
Division:	Gastroenterology			
Street1*:	Stony Brook University			
Street2:	HSC T16-80			
City*:	Stony Brook			
County:	Suffolk			
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117948173			
Phone Number*:	631-444-2119	Fax Number:	E-Mail*: JuanCarlos.Bucobo@stonybrookmedicine.edu	
Credential, e.g., agency login: JCBucobo				
Project Role*: Co-Investigator		Other Project Role Category:		
Degree Type:		Degree Year:		
Attach Biographical Sketch*:		File Name		
		Bucobo__NIHbiosketch_2015.pdf		
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Moro	Middle Name	Last Name*: Salifu	Suffix:
Position/Title*:	Director, Nephrology Fellowship Program			
Organization Name*:	The Research Foundation for SUNY, Downstate Medical Center			
Department:	Medicine			
Division:	Nephrology			
Street1*:	450 Clarkson Ave			
Street2:				
City*:	Brooklyn			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	112030000			
Phone Number*:	718-270-1584	Fax Number:	E-Mail*: moro.salifu@downstate.edu	
Credential, e.g., agency login: morosalifu				
Project Role*: Other (Specify)		Other Project Role Category: Subsite Lead		
Degree Type: MD,MBA,MPH		Degree Year:		
Attach Biographical Sketch*:		File Name		
		Biosketch_Salifu_P20rev2.pdf		
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Laura	Middle Name	Last Name*: Martello-Rooney	Suffix:
Position/Title*:	Director of GI Research			
Organization Name*:	The Research Foundation for SUNY, Downstate Medical Center			
Department:	Medicine			
Division:	GI Research			
Street1*:	450 Clarkson Ave			
Street2:				
City*:	Brooklyn			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	112032012			
Phone Number*:	718-270-1290	Fax Number:	718-270-7201	E-Mail*: laura.martello-rooney@downstate.edu
Credential, e.g., agency login: MARTELLOROONEY				
Project Role*: Other (Specify)			Other Project Role Category: Subsite Co-Investigator	
Degree Type:			Degree Year:	
Attach Biographical Sketch*:			File Name	
			Biosketch_Martello_Rooney__P20Li.pdf	
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Mark	Middle Name	Last Name*: Stewart	Suffix:
Position/Title*:	Professor, Dean Sch Grad Stud			
Organization Name*:	The Research Foundation for SUNY, Downstate Medical Center			
Department:	Physiology and Pharmacology			
Division:	Graduate Studies			
Street1*:	450 Clarkson Ave			
Street2:				
City*:	Brooklyn			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	112032012			
Phone Number*:	718-270-1167	Fax Number:	718-270-3103	E-Mail*: mark.stewart@downstate.edu
Credential, e.g., agency login: mstewart				
Project Role*: Other (Specify)			Other Project Role Category: Subsite Co-Investigator	
Degree Type:			Degree Year:	
			File Name	
Attach Biographical Sketch*:				
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Gerardo	Middle Name Guillermo	Last Name*: Mackenzie	Suffix:
Position/Title*:	Assistant Professor			
Organization Name*:	Stony Brook University			
Department:	Preventive Medicine			
Division:				
Street1*:	Stony Brook University			
Street2:	HSC-T17, room 080			
City*:	Stony Brook			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117948175			
Phone Number*:	631-444-9537	Fax Number:	E-Mail*: Gerardo.Mackenzie@stonybrookmedicine.edu	
Credential, e.g., agency login: GMACKENZIE				
Project Role*: Co-Investigator		Other Project Role Category:		
Degree Type: PHD,BS		Degree Year:		
Attach Biographical Sketch*:		File Name		
		Biosketch_GG_MACKENZIE031115.pdf		
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Shivakumar	Middle Name	Last Name*: Vignesh	Suffix:
Position/Title*:	Chief			
Organization Name*:	SUNY Downstate			
Department:	Medicine			
Division:	Gastroenterology			
Street1*:	450 Clarkson Avenue			
Street2:				
City*:	Brooklyn			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	112030000			
Phone Number*:	718-270-1113	Fax Number:	E-Mail*: shivakumar.vignesh@downstate.edu	
Credential, e.g., agency login: SVIGNESH				
Project Role*: Co-Investigator		Other Project Role Category:		
Degree Type:		Degree Year:		
Attach Biographical Sketch*:		File Name		
		Vignesh_Biosketch_2015_P20.pdf		
Attach Current & Pending Support:				

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2015

End Date\*: 08-31-2016

Budget Period: 1

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Juan	Carlos	Bucubo		Ci-Investigator	0.00	0.3			0.00	0.00	0.00
2.	Gerado		Mackenzie		Co-I	105,786.00	6.0			5,289.00	3,009.00	8,298.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons:		File Name:		Total Senior/Key Person								8,298.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
	Post Doctoral Associates							
	Graduate Students							
	Undergraduate Students							
	Secretarial/Clerical							
0	Total Number Other Personnel	Total Other Personnel					0.00	
					Total Salary, Wages and Fringe Benefits (A+B)			8,298.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
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2. Foreign Travel Costs	0.00
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<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
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2. Stipends	0.00
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3. Travel	0.00
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4. Subsistence	0.00
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5. Other:	
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<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	44,137.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Animal and related cost	3,000.00
<b>Total Other Direct Costs</b>	<b>47,137.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>55,435.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	58.0	11,298.00	6,553.00
2. DownState	61.5	44,137.00	27,144.00
	<b>Total Indirect Costs</b>		<b>33,697.00</b>
<b>Cognizant Federal Agency</b>		Modified Direct Total Cost rate, Agreement dated 02/21/2014 with	
(Agency Name, POC Name, and POC Phone Number)		Department of Health and Human Services, Darryl. W. Mayes,	
		212-264-2069.	

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>89,132.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	<b>File Name:</b>
	P20_Pilot_Project_2_Budget_Justification_031715.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 2

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2016

End Date\*: 08-31-2017

Budget Period: 2

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Juan	Carlos	Bucubo		Ci-Investigator	0.00	0.3			0.00	0.00	0.00
2.	Gerardo		Mackenzie		CO-I	105,786.00	0.6			5,289.00	3,009.00	8,298.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons:		File Name:		Total Senior/Key Person								8,298.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
	Post Doctoral Associates							
	Graduate Students							
	Undergraduate Students							
	Secretarial/Clerical							
0	Total Number Other Personnel	Total Other Personnel					0.00	
					Total Salary, Wages and Fringe Benefits (A+B)			8,298.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	51,217.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Animals and related materials	3,000.00
<b>Total Other Direct Costs</b>	<b>54,217.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>62,515.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	58.0	11,298.00	6,553.00
2. Downstate	61.5	51,217.00	31,498.00
	<b>Total Indirect Costs</b>		<b>38,051.00</b>
<b>Cognizant Federal Agency</b>		Modified Direct Total Cost rate, Agreement dated 2/21/2014with	
(Agency Name, POC Name, and POC Phone Number)		Department of Health and Human Services, Darryl. W. Mayes,	
		212-264-2069.	

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>100,566.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	<b>File Name:</b>
	P20_Pilot_Project_2_Budget_Justification_031715.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 3

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 3

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Juan	Carlos	Bucubo		Ci-Investigator	0.00	0.3			0.00	0.00	0.00
2.	Gerardo		Mackenzie		Co-I	105,786.00	0.6			5,289.00	3,009.00	8,298.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	8,298.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							8,298.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
--------------------------	-------------

**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	51,237.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Animals and related materials	3,000.00
<b>Total Other Direct Costs</b>	<b>54,237.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>62,535.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	58.0	11,298.00	6,553.00
2. DownState	61.5	51,237.00	31,511.00
	<b>Total Indirect Costs</b>		<b>38,064.00</b>
<b>Cognizant Federal Agency</b>		Modified Direct Total Cost rate, Agreement dated 2/21/2014 with	
(Agency Name, POC Name, and POC Phone Number)		Department of Health and Human Services, Darryl. W. Mayes,	
		212-264-2069.	

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>100,599.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name:
	P20_Pilot_Project_2_Budget_Justification_031715.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 4

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2018

End Date\*: 08-31-2019

Budget Period: 4

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Juan	Carlos	Bucubo		Ci-Investigator	0.00	0.3			0.00	0.00	0.00
2.	Gerardo		MacKenzie		Co-I	105,786.00	0.6			5,289.00	3,009.00	8,298.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons:		File Name:		Total Senior/Key Person								8,298.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
	Post Doctoral Associates							
	Graduate Students							
	Undergraduate Students							
	Secretarial/Clerical							
0	Total Number Other Personnel	Total Other Personnel					0.00	
					Total Salary, Wages and Fringe Benefits (A+B)			8,298.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	0.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	51,261.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Animals and related material	3,000.00
<b>Total Other Direct Costs</b>	<b>54,261.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>62,559.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	58.0	11,298.00	6,553.00
2. Downstate MTDC	61.5	51,261.00	31,525.00
<b>Total Indirect Costs</b>			<b>38,078.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 2/21/2014 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl. W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>100,637.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	<b>File Name:</b>
	P20_Pilot_Project_2_Budget_Justification_031715.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## Budget Justification – Pilot Project P2 (Institutional)

### A. Key Personnel:

1. **Gerardo Mackenzie, Ph.D.** Contact PI. **Dr. Mackenzie** will devote 0.6 calendar months to this project at his salary and fringes. He is a biochemist and cancer biologist scientist, with considerable expertise in pancreatic cancer, experimental therapeutics and chemoprevention. He is a young URM NCI funded investigator, who recently joined the Stony Brook University faculty as Assistant Professor of Preventive Medicine. He will lead aim 3 of pilot project 2 (tumor progression studies) and will work closely with **Dr. Tuveson** to develop the pancreatic organoid model at SUNY Stony Brook.
2. **Juan Carlos Bucobo, M.D.** co-I. **Dr. Bucobo** will devote 0.24 calendar months of uncompensated effort to this project. He is Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology and Director of Endoscopy at Stony Brook University Hospital. He is a URM interventional endoscopist who was instrumental in developing the protocol for obtaining ex vivo FNBs used by Dr. Tuveson's laboratory that led to the preliminary data for the pilot project. He also coordinated with the two other interventional endoscopists in the GI Division to pilot the first in vivo EUS-FNB core biopsies from a patient with pancreatic cancer. **Dr. Bucobo** is a member of the American Society of Gastrointestinal Endoscopy Diversity Committee. He has a long standing interest in cancer health disparities and is examining the role of bilingual student patient navigators in boosting colon cancer screening. He will assist **Dr. Vignesh**, Chief of the Division of Gastroenterology and Hepatology, and noted endoscopic oncologist, and **Dr. Martello Rooney** with launching the EUS-FNB protocol at SUNY Downstate as they develop a parallel GI Biobank.

**B. Other Personnel:** none

**C. Equipment:** none.

**D. Animal studies:** \$3,000/year is requested to cover animal ordering, housing and other animal study related costs.

**E. Travel:** none

### F. Other Expenses:

Subcontract: \$51,196 is requested in direct costs from SUNY Downstate for pilot project **P2**.

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	Totals (\$)	
Section A, Senior/Key Person		33,192.00
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		33,192.00
Section C, Equipment		0.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		209,852.00
1. Materials and Supplies	0.00	
2. Publication Costs	0.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	197,852.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	12,000.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		243,044.00
Section H, Indirect Costs		147,890.00
Section I, Total Direct and Indirect Costs (G + H)		390,934.00
Section J, Fee		0.00

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2015

End Date\*: 08-31-2016

Budget Period: 1

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Laura		Martello-Rooney		Co-Investigator	65,000.00	0.6			3,250.00	1,387.00	4,637.00
2.	Shivakumar		Vignesh		Co-Investigator	0.00	0.6			0.00	0.00	0.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	4,637.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
1	Graduate Students	12.0			28,000.00	0.00	28,000.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Total Number Other Personnel					Total Other Personnel	28,000.00
					Total Salary, Wages and Fringe Benefits (A+B)		32,637.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
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2. Foreign Travel Costs	0.00
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<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
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2. Stipends	0.00
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3. Travel	0.00
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4. Subsistence	0.00
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5. Other:	
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<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	7,500.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Trainee Field Work Costs	4,000.00
<b>Total Other Direct Costs</b>	<b>11,500.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>44,137.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	61.5	44,137.00	27,144.00
<b>Total Indirect Costs</b>			<b>27,144.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 1/31/13 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>71,281.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	
	File Name: P20_grant- Budget_justification_Pilot_Project_2_2015.pdf (Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 2

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2016

End Date\*: 08-31-2017

Budget Period: 2

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Laura		Martello-Rooney		Co-Investigator	65,000.00	0.6			3,250.00	1,467.00	4,717.00
2.	Shivakumar		Vignesh		Co-Investigator	0.00	0.6			0.00	0.00	0.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	4,717.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
1	Graduate Students	12.0			28,000.00	0.00	28,000.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Total Number Other Personnel					Total Other Personnel	28,000.00
Total Salary, Wages and Fringe Benefits (A+B)							32,717.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	14,500.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Trainee Field Work Costs	4,000.00
<b>Total Other Direct Costs</b>	<b>18,500.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>51,217.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	61.5	51,217.00	31,498.00
<b>Total Indirect Costs</b>			<b>31,498.00</b>
<b>Cognizant Federal Agency</b>		Modified Direct Total Cost rate, Agreement dated 1/31/13 with	
(Agency Name, POC Name, and POC Phone Number)		Department of Health and Human Services, Darryl W. Mayes,	
		212-264-2069.	

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>82,715.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: P20_grant- Budget_justification_Pilot_Project_2_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 3

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 3

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Laura		Martello-Rooney		Co-Investigator	65,000.00	0.6			3,250.00	1,487.00	4,737.00
2.	Shivakumar		Vignesh		Co-Investigator	0.00	0.6			0.00	0.00	0.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	4,737.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
1	Graduate Students	12.0			28,000.00	0.00	28,000.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Total Number Other Personnel					Total Other Personnel	28,000.00
Total Salary, Wages and Fringe Benefits (A+B)							32,737.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:**    ☐ Project    ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
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**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:**    File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
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2. Foreign Travel Costs	0.00
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<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
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2. Stipends	0.00
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3. Travel	0.00
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4. Subsistence	0.00
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5. Other:	
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<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	14,500.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Trainee Field Work Costs	4,000.00
<b>Total Other Direct Costs</b>	<b>18,500.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>51,237.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	61.5	51,237.00	31,511.00
<b>Total Indirect Costs</b>			<b>31,511.00</b>
<b>Cognizant Federal Agency</b>	Modified Direct Total Cost rate, Agreement dated 1/31/13 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069.		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>82,748.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	
	File Name: P20_grant- Budget_justification_Pilot_Project_2_2015.pdf (Only attach one file.)

RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 4

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2018

End Date\*: 08-31-2019

Budget Period: 4

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Laura		Martello-Rooney		Co-Investigator	65,000.00	0.6			3,250.00	1,511.00	4,761.00
2.	Shivakumar		Vignesh		Co-Investigator	0.00	0.6			0.00	0.00	0.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:											Total Senior/Key Person	4,761.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
1	Graduate Students	12.0			28,000.00	0.00	28,000.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Total Number Other Personnel					Total Other Personnel	28,000.00
Total Salary, Wages and Fringe Benefits (A+B)							32,761.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
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**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	14,500.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Trainee Field Work Costs	4,000.00
<b>Total Other Direct Costs</b>	<b>18,500.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>51,261.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	61.5	51,261.00	31,525.00
<b>Total Indirect Costs</b>			<b>31,525.00</b>
<b>Cognizant Federal Agency</b>		Modified Direct Total Cost rate, Agreement dated 1/31/13 with	
(Agency Name, POC Name, and POC Phone Number)		Department of Health and Human Services, Darryl W. Mayes,	
		212-264-2069.	

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>82,786.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: P20_grant- Budget_justification_Pilot_Project_2_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## **Feasibility Studies to Build Collaborative Partnerships in Cancer Research (P20)**

### **Feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research**

#### **BUDGET JUSTIFICATION – Pilot Project 2**

##### **PERSONNEL**

Laura Martello-Rooney, PhD: Co-Investigator (0.6 calendar months, 5% effort, Years 1-4)  
Dr. Martello-Rooney, Research Assistant Professor, is the Director of GI Research and oversees the research activities of the Division of Gastroenterology & Hepatology. Dr. Martello-Rooney will oversee all aspects of the Pilot Research Projects on the SUNY Downstate campus, including training from CSHL on pancreatic organoid generation.

Shivakumar Vignesh, MD: Co-Investigator (0.6 calendar months, 5% effort, Years 1-4)  
Dr. Vignesh, Associate Professor of Medicine, is the Chief of the Division of Gastroenterology & Hepatology. Dr. Vignesh is trained as an Interventional Endoscopist and will oversee the collection of pancreatic fine-needle biopsies and the annotation of the samples.

Graduate Student (TBD) (12.0 calendar months, 100% effort, Years 1-4)  
The Graduate Student will assist with biospecimen collection and annotation, join CSHL training on pancreatic organoid generation, be involved with tumor analysis and participate in cancer disparities training programs.

##### **OTHER DIRECT COSTS**

##### **SUPPLIES                      \$7,500 (Year 1)/\$14,500 (Years 2-4)**

We are requesting funds for tumor collection supplies such as transport medium, PBS, centrifuge tubes, scalpels, accutase and antibiotics; for cell culture supplies such as medium, serum, antibiotics, cell culture dishes/plates, pipets, centrifuge tubes, cryovials, freezing medium, storage boxes, CO2 tanks, liquid nitrogen; for in vitro assay supplies such as antibodies for marker staining, cell proliferation testing, migration/invasion assays, chemosensitivity testing.

##### **OTHER EXPENSES                      \$4,000**

Trainees field work costs (Years 1-4 \$4,000): We are requesting funds to support trainees involved in outreach related to screening, recruitment and retention activities for Aim 1 of the grant.

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	Totals (\$)	
Section A, Senior/Key Person		18,852.00
Section B, Other Personnel		112,000.00
Total Number Other Personnel	4	
Total Salary, Wages and Fringe Benefits (A+B)		130,852.00
Section C, Equipment		0.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		67,000.00
1. Materials and Supplies	51,000.00	
2. Publication Costs	0.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	16,000.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		197,852.00
Section H, Indirect Costs		121,678.00
Section I, Total Direct and Indirect Costs (G + H)		319,530.00
Section J, Fee		0.00

## PHS 398 Cover Page Supplement

OMB Number: 0925-0001

## 1. Project Director / Principal Investigator (PD/PI)

Prefix:

First Name\*: Ellen

Middle Name:

Last Name\*: Li

Suffix:

## 2. Human Subjects

Clinical Trial?      ☒ No      ☐ YesAgency-Defined Phase III Clinical Trial?\*      ☐ No      ☐ Yes

## 3. Permission Statement\*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes      ☐ No

## 4. Program Income\*

Is program income anticipated during the periods for which the grant support is requested?      ☐ Yes      ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount (\$)*	Source(s)*
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

## PHS 398 Cover Page Supplement

### 5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?\*      ☒ No      ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: [http://grants.nih.gov/stem\\_cells/registry/current.htm](http://grants.nih.gov/stem_cells/registry/current.htm). Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s):      ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

### 6. Inventions and Patents (For renewal applications only)

Inventions and Patents\*:      ☐ Yes      ☐ No

If the answer is "Yes" then please answer the following:

Previously Reported\*:      ☐ Yes      ☐ No

### 7. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name\*:

Middle Name:

Last Name\*:

Suffix:

☐ Change of Grantee Institution

Name of former institution\*:

## PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

<b>1. Introduction to Application</b> <small>(for RESUBMISSION or REVISION only)</small>	P2Introduction_eli_ht_eli031615.pdf
<b>2. Specific Aims</b>	P2_Specific_Aims_Final.pdf
<b>3. Research Strategy*</b>	P2_Research_Strategy_FINAL_031815.pdf
<b>4. Progress Report Publication List</b>	
<b>Human Subjects Sections</b>	
<b>5. Protection of Human Subjects</b>	P2_Protection_of_Human_Subjects_Final.pdf
<b>6. Inclusion of Women and Minorities</b>	P2_IOW_Final.pdf
<b>7. Inclusion of Children</b>	P2_IOC_Final.pdf
<b>Other Research Plan Sections</b>	
<b>8. Vertebrate Animals</b>	Pilot2_VERTEBRATE_ANIMALS_Section_GGM_03-17-15.pdf
<b>9. Select Agent Research</b>	
<b>10. Multiple PD/PI Leadership Plan</b>	
<b>11. Consortium/Contractual Arrangements</b>	
<b>12. Letters of Support</b>	Proj2_LOS.pdf
<b>13. Resource Sharing Plan(s)</b>	ResourcePlan_Proj2.pdf
<b>Appendix (if applicable)</b>	
<b>14. Appendix</b>	

## INTRODUCTION - PILOT RESEARCH PROJECT 2 (P2)

We have made extensive changes in Pilot Research Project 2 in response to the reviewers' thoughtful comments, which was rated unanimously as "Moderate Impact". We were gratified that the reviewers felt that "Understanding the genetic factors that contribute to the disease (pancreatic cancer) in this under-represented minority (African American) population is highly significant", the *"use of organoids is novel"* and that *"The involved investigators are well qualified for conducting the proposed study..."*.

In response to the reviewers' concern that the number of samples analyzed will be too small to generate any meaningful results we have revised **Specific Aim 1** to align more closely with the overall objective of PAR-14-152 entitled "Feasibility Studies to Build Collaborative Partnerships in Cancer Research". The major objective of **Aim 1** of the revised **P2** is now to determine the feasibility of developing a SUNY Downstate GI Biobank that can support the collection of URM EUS-FNB samples that can be successfully grown as organoids, rather than identifying biological markers that are associated with the poorer clinical outcomes of African American compared to Caucasian pancreatic tumors. We have clarified the number of total URM pancreatic cancer patients to be recruited at SUNY Downstate as 10 each year (total = 40). The preliminary data generated from this P20 award will hopefully put us in position to apply for much larger awards in the future to address the latter goal, by conducting a detailed comparative genomic and epigenomic analysis of URM and non-URM pancreatic cancer organoids originally detailed in the initial P2 application.

In response to reviewer's concerns that **Dr. Martello Rooney's** involvement "will presumably not involve tissues from FNAs", we have added **Dr. Shivakumar Vignesh** as a SUNY Downstate co-I. Since the initial submission of the P20 application, **Dr. Vignesh** was appointed Chief of the Division of Gastroenterology from the Moffitt Cancer Center in Tampa, Florida where he directed the Advanced Endoscopic Oncology fellowship. Because of the limited funding provided in this award, the **P2** budget is directed primarily toward collection of URM samples at SUNY Downstate. We are seeking other funding agencies to support generation of predominantly non-URM organoids by SUNY Stony Brook in collaboration with CSHL.

In response to the criticism that "plans for the potential participation of trainees are not adequately described.", we have integrated the **P2** project more closely with the Training and Education Program (TEP), since **Dr. Martello-Rooney** has identified a Hispanic SUNY Downstate first year graduate student, who is interested in working on the pancreatic organoid model, who would also be a likely candidate for our scholars in the new BioMedical Sciences in Cancer Health Disparities program proposed in the TEP section of this proposal.

In response to a reviewer's comment that "...the proposed studies would not greatly expand the current scope of work" we would like to clarify that our preliminary attempts on growing pancreatic organoids from EUS-FNB are not currently supported by any extramural funds. Dealing with the regulatory issues in conducting this protocol is costly and time consuming. In fact the first SUNY Stony Brook in vivo EUS-FNB derived organoids were grown only two weeks before the submission of this revised proposal. This collaborative effort was supported by **Dr. Li's** discretionary funds in providing the study coordinator (IRB approval, identification of patient, consenting of patient) and the technician/runner (collection during procedure, rapidly transport of sample to CSHL within two hours of the procedure) and **Dr. Tuveson's** discretionary funds in providing the costly reagents required to grow the organoids.

To address reviewer concerns about whether EUS-FNB derived organoids will be representative of the larger tumor, we propose to compare whole genome copy number variants (CNV) in the EUS-FNB derived organoid compared to organoids generated from a larger cross sectional sample of the same pancreatic cancer (i.e. collection from surgically resectable pancreatic cancers) in the revised **Specific Aim 2**.

The reviewers correctly pointed out that the organoid model focuses primarily on epithelial cells and may miss the contribution of the microenvironment. **Dr. Mackenzie**, a young Hispanic NCI funded investigator in pancreatic cancer at SUNY Stony Brook will replace Dr. Li as the SUNY contact PI in the revised **P2**. As detailed in the new **Specific Aim 3**, he will focus on comparing molecular alterations in neoplastic cells, and cellular differences that occur after heterotopic transplantation between URM (originating from SUNY Downstate) and non-URM (existing non-URM CSHL preparations and additional originating from SUNY Stony Brook) derived organoids matched for cancer stage and other covariates such as smoking, alcohol, diabetes and obesity. Implanted organoids undergo neoplastic progression, with a rich tumor microenvironment that recapitulates some aspects of the human tumor such as desmoplastic formation. This change should also address reviewer concerns that *"Pilot Project 2 does not appears to involve SUNY investigators except for methodology for acquiring tissue from Fine Needle Aspirates, participation in conducting the research appears to be limited to data sharing."*

## **Specific Aims**

### **Hypothesis**

Genetic and gene expression alterations underlie the increased incidence, mortality, and treatment resistance observed in underrepresented minorities (URMs). A new tissue model system, organoids, will allow the evaluation of the cell autonomous contribution to the increased risk of pancreatic cancer in URMs.

#### **Specific Aim 1: Preparation of URM pancreatic cancer organoids**

To study the cell intrinsic properties of URM pancreatic cancer, we will establish a cohort of endoscopic biopsy-derived organoids from URM patients. Accordingly, we have adapted our organoid culture system to support the growth and expansion of limited tissue samples obtained endoscopically. These organoids will then be evaluated at the molecular and cellular level to reveal any innate features of URM neoplastic cells.

#### **Specific Aim 2: Molecular characterization of URM pancreatic cancer organoids**

To delineate the molecular properties of URM pancreatic cancer cells, the organoids derived from URM patients will be analyzed using next generation sequencing. Both genetic (DNA sequencing) and gene expression (RNA sequencing) information will be gathered. Using this information, we will establish the molecular similarities and differences between URM and non-minority populations with pancreas cancer. This information will be correlated to clinical outcome and ethnicity to reveal underlying characteristics of URM pancreatic cancer.

#### **Specific Aim 3: Tumor progression studies of URM pancreatic cancer organoids**

To determine whether there are innate cell biological differences between URM and non-URM pancreatic cancer cells, URM pancreatic cancer organoids will be transplanted orthotopically and tumor progression will be compared to non-URM samples. The kinetics and extent of tumor progression will be compared between the URM and non-URM organoids.

## Pilot Research Project 2 (P2) –Research Strategy

### 1. Significance.

**1A. Pancreatic Cancer Health Disparities.** Pancreatic cancer holds the worst survival rate of the common malignancies, in part due to the poor response to treatments [1, 2]. The clinical options available to pancreatic cancer (PDA) patients are determined by the extent of disease progression, and unfortunately the vast majority of patients are ineligible for curative surgical approaches [3-5]. African Americans have a higher incidence of, and mortality from, pancreatic cancer. African Americans have a relative risk of 1.7 for men and 1.5 for women [6-8]. While this **P2** is focused on racial/ethnic differences in pancreatic cancer, it is critical that potential confounding covariates be rigorously recorded and included in the final analysis. For example racial/ethnic differences in socioeconomic status are likely to relate to racial ethnic differences in detection and treatment of pancreatic cancers [9]. While some of the biological differences may directly relate to genetic factors directly affecting pancreatic cancer progression, others may relate to potential differences in exposure to environmental factors such as smoking or alcohol [10-12]. African Americans are also at higher risk for diabetes and obesity, two conditions associated with elevated risk for pancreatic cancer [12-14].

**1B. Overcoming Barriers to Collecting Under Represented Minorities (URM) Pancreatic Cancer Specimens Linked to Longitudinal Clinical Metadata.** Limiting the analysis of PDA tissue to only those patients that go for curative resection (20%) significantly reduces our ability to advance our knowledge of this disease; because studies that rely only on surgically resected specimens represent a biased sampling of all pancreatic cancers. Representation of African American patients in repositories of surgically resected specimens may be compromised because African Americans are offered surgical options less often and are more likely to refuse surgery if recommended [15, 16]. While it has been claimed that African Americans are less willing to participate in contributing biospecimens, a more recent study concludes that the major barrier may relate to medical researchers being less likely to approach African Americans for contribution of specimens [17]. This could also relate to lack of resources at medical centers serving URM predominant populations for supporting the labor intensive and consequently costly collection efforts required to sustain Biobank operations. In this revised **P2** we propose to address these barriers by developing a living Biobank of pancreatic cancer organoids from endoscopic ultrasound guided fine needle core biopsies (EUS-FNB). This cutting edge approach will allow us to sample unresectable pancreatic cancers as well as surgically resectable pancreatic cancers. **Dr. Tuveson's** laboratory has been at the forefront in developing this model system, which will be described in further detail in the following **Innovations** section. Since the submission of the original P20 application in May 2014, SUNY Stony Brook interventional endoscopists, led by **Dr. Bucobo**, have been working closely with the SUNY Stony Brook GI Biobank and **Dr. Tuveson's** to optimize the protocol for growing pancreatic organoids from such limited amounts of tissue. However the SUNY Stony Brook patient population has relatively low representation of African Americans (~5%). Consequently the main objective of the P2 project in this revised P20 application, as described in **Aim 1**, is to establish the feasibility of developing a parallel SUNY Downstate GI Biobank (Drs. **Martello-Rooney** and **Vignesh**) that can support the collection of EUS-FNB samples to generate URM pancreatic organoids. Over 70% of the patients seen at the SUNY Downstate and neighboring King's County Hospital are African American. URM patient recruitment will be facilitated by the Brooklyn Health Disparity Center led by **Dr. Moro Salifu** (see Administrative Core), which has developed close ties with community leaders.

**1C. Mentorship of Trainees and Junior Faculty Investigators interested in Pancreatic Cancer Health Disparities.** Participation of trainees in the **P2** project provides an excellent opportunity for undergraduate students, medical students, graduate students and clinical fellows and postdoctoral fellows to participate in clinical translational projects related to Cancer Health Disparities. The **P2** project will be closely integrated with the novel **Scholars in BioMedical Sciences in Cancer Health Disparities (SBMS-CHD)** program being developed by the revised P20 Training and Education Program. In fact **Dr. Martello-Rooney** has identified a URM SUNY Downstate graduate student who will be joining her laboratory to work on pancreatic cancer health disparity. We anticipate that this graduate student would be an excellent candidate for the SBMS-CHD program, which would support her taking courses at CSHL and rotating in **Dr. Tuveson's** laboratory to learn the methodology for growing pancreatic organoids. Finally, the long-range goal of the **P2** program is to adapt this organoid technology at SUNY Stony Brook and Downstate. Thus **Dr. Tuveson** will serve as a senior research mentor to Drs. **Mackenzie** and **Martello-Rooney**.

## **2. Innovation**

**2A. Generation of Pancreatic Organoids from EUS FNB Pancreatic Cancer Samples.** The Tuveson laboratory has developed a novel, ex vivo, pancreatic organoid model system [18]. This new three-dimensional, cell culture model system facilitates the rapid isolation and establishment of organoid lines from both normal and malignant human pancreatic tissue. In **Aim 1**, we will focus primarily on growing organoids from malignant pancreatic tissue. In previous studies the Tuveson laboratory has demonstrated while both N (Normal tissue) and T (Tumor tissue) organoids express markers of the pancreatic ductal lineage, T organoids express elevated levels of genes that correlate with tumorigenesis. Furthermore, following the transplantation of T organoids into immune-compromised mice, they recapitulate the neoplastic histopathology from which they were originally derived. Therefore, the pancreatic ductal organoids reflect the molecular characteristics of normal and malignant epithelial cells in vivo. Using this novel culture system, organoids can be rapidly expanded within two weeks instead of the months it may take to establish patient derived xenografts. This more rapid turnaround time is very important for future potential use in precision medicine since progression of advanced pancreatic cancer also takes place over months. In **Aim 2** we will molecularly characterize newly established organoids using next generation sequencing of DNA and mRNA. These organoids are also amenable to genetic manipulation through viral transduction or CRISPR/Cas mediated gene editing, and will thus be useful for future studies of genetic and epigenetic drivers of pancreatic cancer. Transplanted tumor organoids develop a surrounding desmoplastic reaction and form mucin-containing low-grade PanIN as well as high-grade PanIN with microinvasive PDA, which is in contrast to the lack of stromal reaction observed upon transplantation of two-dimensional human PDA cell lines. Using this approach, tumor progression of URM and non-URM PDA will be addressed in **Aim 3**. While our **P2** will focus on the generation of T-organoids rather than N-organoids from URM patients, we would also like to mention that N-organoids have an advantage over previous culture systems for normal pancreatic tissue. Previous culture systems enabled temporary isolation of normal pancreatic epithelial cells, which undergo senescence and fail to contribute to the normal pancreatic architecture upon transplantation [19, 20].

### **2B. Using the P2 Project to Drive Development of the SUNY Downstate GI Biobank Collection Process.**

By developing the SUNY Downstate GI Biobank as described in **Aim 1**, in a project driven manner that engages clinicians such as Drs. **Vignesh** and **Bucobo** at the outset, we will insure efficient recruitment of patients scheduled for EUS-FNB procedures for diagnosing pancreatic masses for this project. As discussed below, the focus of the **P2** will be on chemo- and radiation-naïve pancreatic cancer patients. These clinicians are also engaged in the care of unresectable pancreatic cancers, which may require multiple endoscopic procedures to relieve pain or to relieve obstructive jaundice. These clinicians are well placed for collecting longitudinal clinical data as well as possibly collecting serial tissue biopsies at subsequent encounters as the patients complete treatment for their pancreatic cancers. The clinicians also play a critical role in formulating the critical data elements (e.g. smoking, alcohol use, diabetes mellitus, obesity) and to devise a controlled vocabulary across the two SUNY campuses (see Administrative Core). These clinical covariates will need to be included in the final analysis of URM vs. non-URM pancreatic cancers. Also using identical data elements and controlled vocabulary will facilitate future collaborative studies utilizing patient based samples stored at the SUNY Stony Brook and Downstate GI Biobanks.

## **3. Background**

PDA is a highly aggressive and lethal malignancy with a median survival of 6 months and a 5-year survival of <5% [1, 2]. Several factors account for this poor outcome, including advanced stage of disease at diagnosis and therapeutic resistance [3-5]. In order to permit improvements in pancreatic cancer patient outcome, we must understand the molecular alterations driving early-stage and recurrent disease. In particular, African Americans and other URM have a higher incidence of, and mortality from, pancreatic cancer, resulting in an increased relative risk of 1.7 for men and 1.5 for women [6-8]. While Hispanic Americans do not exhibit the same level of elevated risk as African Americans, both populations are at higher risk for diabetes and obesity, two conditions associated with elevated risk for pancreatic cancer. Accordingly, our proposed work will first address the genetic and transcription differences that influence pancreatic cancer incidence and mortality specifically in African American and Hispanic American patients. We hypothesize that in addition to the increased incidence of KRAS<sup>G12V</sup> driver mutations observed in the African American population [21], there are other genetic differences that underlie the heightened malignancy of this disease in specific racial populations. These alterations may also influence other disease states that are associated with increased pancreatic cancer risk, such as diabetes, obesity, and chronic pancreatitis. Understanding these differences may identify new

diagnostic and therapeutic targets that are more efficient at detecting and treating pancreatic cancer in these at-risk populations.

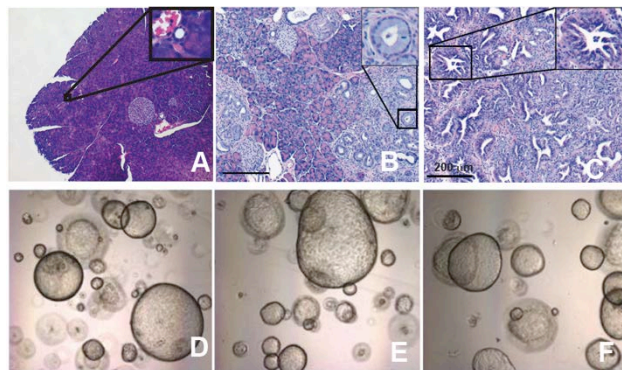
Knowledge of genetic and gene-expression changes associated with PDA incidence and mortality in URM will allow advancements in early detection as well as provide novel targets for therapeutic intervention. Pancreatic carcinogenesis proceeds through a series of accumulating genetic alterations and morphological changes, accompanied by a pronounced stromal reaction. PDA is characterized by frequent activating mutations in *KRAS* (90-95%) and inactivation of the tumor suppressors *CDKN2A* (*P16/INK4A*), *TRP53* and *SMAD4* [22, 23]. Importantly, the substantial toxicity noted in a recent clinical trial that simultaneously targeted the MAPK and PI3K Ras effector pathways emphasizes the need to identify novel therapeutic avenues for pancreatic cancer [24]. In order to investigate the biology of PDA *in vivo*, we previously generated a mouse model of early stage PDA by conditionally expressing an endogenous *Kras*<sup>LSL-G12D</sup> allele in developing pancreatic tissues through the use of pancreas-specific Cre recombinase alleles [25]. *Kras*<sup>LSL-G12D</sup>; *Pdx-cre* ("KC") mice contained ductal lesions that mirrored human pancreatic intraepithelial neoplasms (PanINs), and stochastically developed metastatic PDA [25]. To promote the rapid onset of PDA, additional mutations in tumor suppressor genes are incorporated to generate robust mouse PDA models for the exploration of medical applications and tumor biology [26-31]. For example, *Kras*<sup>LSL-G12D</sup>; *Trp53*<sup>LSL-R172H</sup>; *Pdx-cre* ("KPC") mice provided the insight that both murine and human PDA possessed a deficient vasculature that could impair drug delivery [32]. KC and KPC mice also revealed the importance of cell-intrinsic and microenvironmental survival cues, including Notch and Connective Tissue Growth Factor, for chemotherapy resistance [33-36].

Recently, we have developed pancreatic ductal organoids as a new model system to study pancreatic cancer biology and therapy [18]. These *ex vivo* organoids will allow a systematic investigation into the genetic alterations harbored by pre-malignant lesions, with the goal of identifying novel biomarkers and therapeutic targets. Pancreatic ductal organoids can be prepared from normal, pre-malignant and malignant murine or human pancreatic tissues. Upon culture in semisolid media, organoids grow as hollow, cystic structures with persistent proliferation. Viral transduction or gene editing approaches such as CRISPR/Cas targeting [37, 38] can be used for genetic manipulation, including gene knockdown, overexpression or mutation. The phenotypic effects of these manipulations can then be evaluated in culture or following orthotopic transplantation. The strength of this approach lies in the isolation of ductal epithelial cells, a minority of the pancreatic tissue, allowing molecular approaches that are not feasible when using whole tissues. Furthermore, the organoids provide a model by which to directly compare normal, pre-malignant and malignant cells for response to genetic or pharmacological modulation, allowing optimization prior to *in vivo* evaluation.

A major innovation of the pancreatic organoid system is the ability to maintain ductal structures from normal pancreas in culture. This allows a direct comparison of genomic and expression signatures to therapeutic response of the patient as well as their matched malignant organoid lines. In particular, the efficiency and reliability of organoid line generation will enable the iterative isolation of organoid lines from the same patient from the earliest stages of disease to metastases. Finally, 3D culture of epithelial cells has been shown to more accurately reflect the gene expression profiles and phenotypic characteristics of the intact organ than standard monolayer cell culturing [39]. We will exploit these advantages to characterize the molecular and cellular properties of normal and tumor-derived URM organoids.

#### 4. Preliminary results

To demonstrate the applicability of the organoid model system for systematic molecular analyses, we performed RNA-seq on mouse Normal-derived (N), Pan-IN-derived (P) and Tumor-derived (T) organoids (**Fig. 1**) [18]. Reads were aligned to the mm9 version of the mouse genome, including RefSeq definitions of known splice junctions, using the STAR algorithm [40] with default settings that allow 10 maximum mismatches and 10 multiple alignments per read. HTSeq-count was used to measure read abundance and DESeq was used for differential analysis [41]. Comparisons between the samples revealed subsets of genes differentially expressed in N, P and T organoids (**Fig. 2A**). Analysis of the overlapping gene sets identified genes up or downregulated in both P and T organoids, as well as those up or downregulated in either P or T alone (**Fig. 2B**). Interestingly,

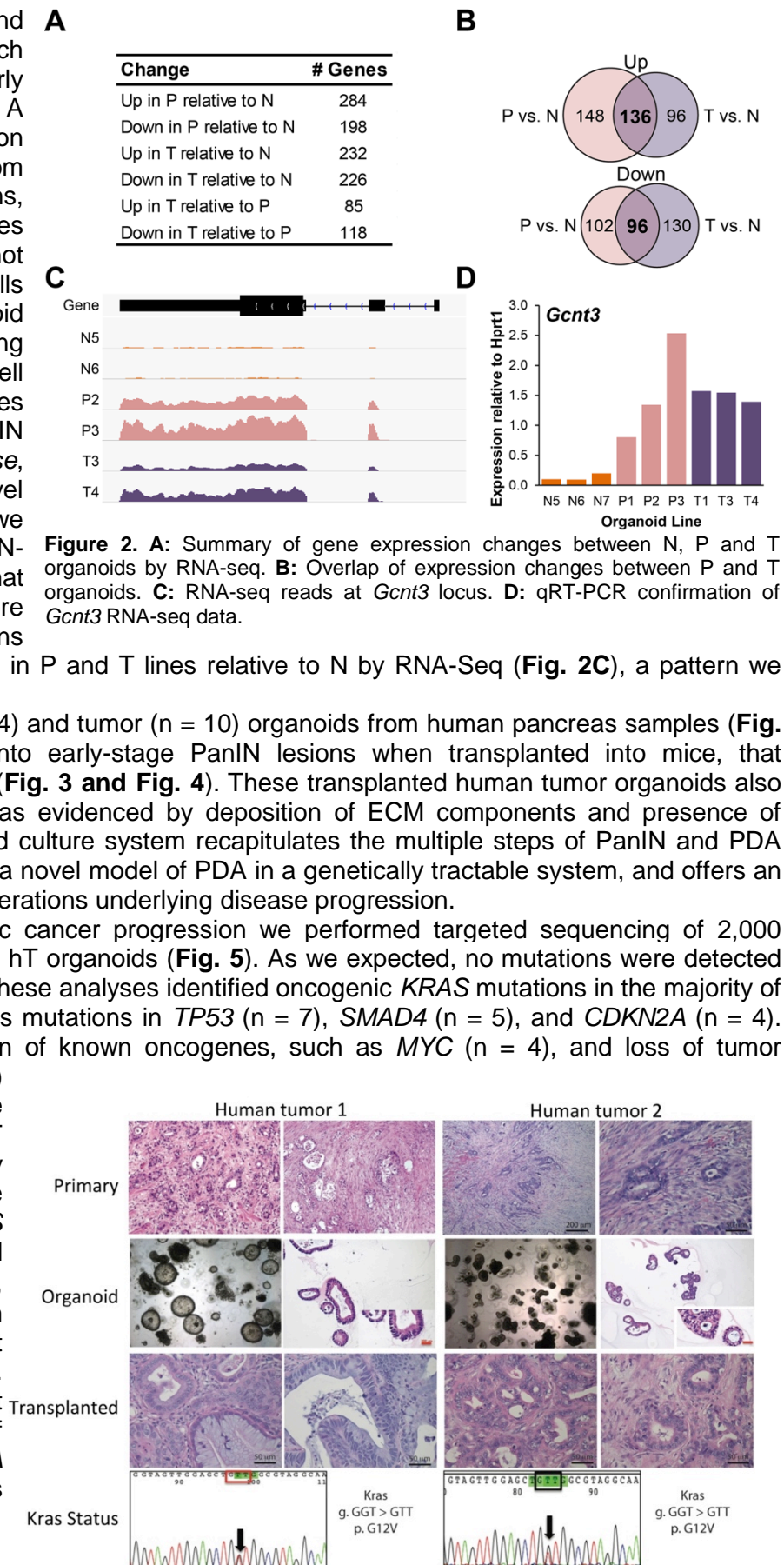


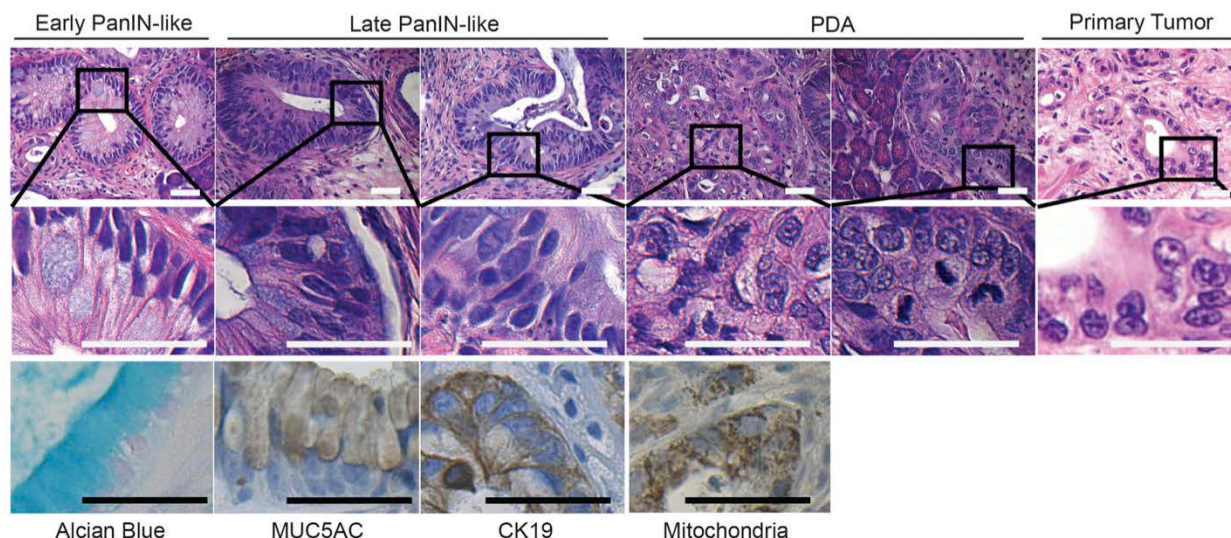
**Figure 1.** Mouse pancreatic tissues from Normal (A), PanIN (B) and Tumor (C) were used to isolate the corresponding organoid lines (D-F). Scale bar 200µm.

many genes were non-overlapping in P and T relative to N, providing clues as to which genes or pathways may represent early and late events during tumorigenesis. A recent study performed gene expression profiling on PanINs isolated from prophylactic pancreatectomy specimens, identifying 76 commonly deregulated genes [42]. However, samples were not microdissected and therefore included cells from the surrounding stroma. The organoid system has the advantage of determining solely the contribution of the epithelial cell compartment. Our analysis recorded genes previously reported to be involved in PanIN and PDA, including *Gcnt3*, *Trf*, *Ctse*, *S100a7a* and *Ambp*, as well as novel candidates. As an initial target we investigated *Gcnt3*, a  $\beta$ 1,6-N-acetylglucosamine-transferase that catalyzes the formation of core 2 and core 4 O-glycans on mucin-type glycoproteins [43]. *Gcnt3* was found to be upregulated in P and T lines relative to N by RNA-Seq (Fig. 2C), a pattern we confirmed by qRT-PCR (Fig. 2D).

We have also generated normal (n = 4) and tumor (n = 10) organoids from human pancreas samples (Fig. 3). Tumor organoids initially develop into early-stage PanIN lesions when transplanted into mice, that progressed to PDA over several months (Fig. 3 and Fig. 4). These transplanted human tumor organoids also induce a robust desmoplastic reaction, as evidenced by deposition of ECM components and presence of stromal cells (Fig. 4). Thus, our organoid culture system recapitulates the multiple steps of PanIN and PDA upon orthotopic transplantation, provides a novel model of PDA in a genetically tractable system, and offers an alternative means to probe the genetic alterations underlying disease progression.

To characterize events in pancreatic cancer progression we performed targeted sequencing of 2,000 cancer-associated genes on both hN and hT organoids (Fig. 5). As we expected, no mutations were detected in the hN organoid cultures. Importantly, these analyses identified oncogenic *KRAS* mutations in the majority of tumor-derived samples (n = 8), as well as mutations in *TP53* (n = 7), *SMAD4* (n = 5), and *CDKN2A* (n = 4). Furthermore, we also noted amplification of known oncogenes, such as *MYC* (n = 4), and loss of tumor suppressors, including *TGFBR2* (n = 3) and *DCC* (n = 5). Importantly, the same *KRAS* mutations observed in several hT organoids were confirmed in the primary PDA from which they were derived. The allele frequency of oncogenic *KRAS* variants in hT1–hT5 and hFNA2 ranged from ~50–100%. In contrast, the *KRAS*G12V allele frequency in hFNA1 was only 1%, which may result from coexistence of wild-type ductal cells. Although *KRAS* mutations were not detected in hT8, the presence of mutations in known PDA genes (*ARID1A* and *MLL3*) suggests that hT8 contains malignant cells.





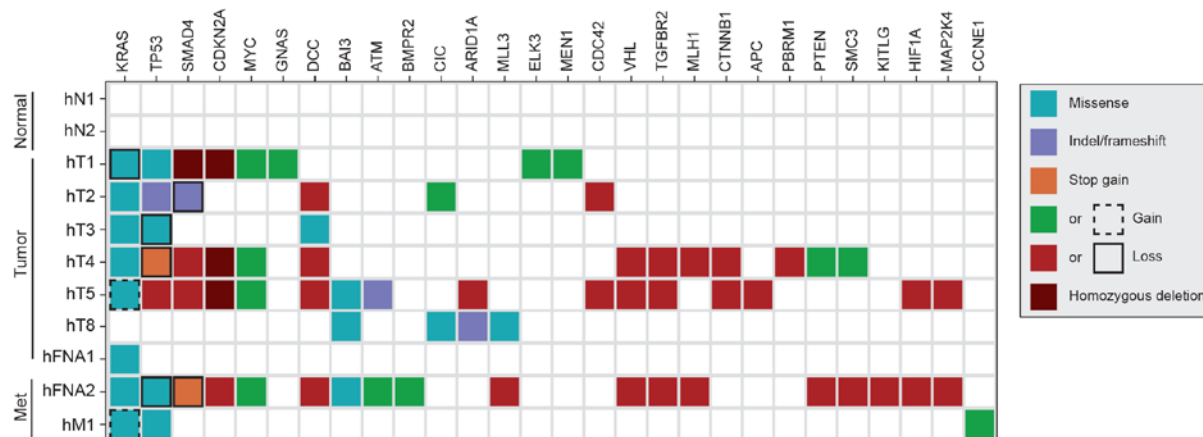
**Figure 4.** Following orthotopic transplantation into *Nu/Nu* mice, hT4 organoids formed low- and high-grade PanIN-like structures within one month ( $n = 2/2$  mice). PDA was observed at later time points ( $n = 2/2$  mice). Histology of the primary tumor is included (right-most panels). Mucinous metaplasia is highlighted by Alcian Blue staining as well as MUC5AC and CK19 IHC. IHC staining for human mitochondrial protein confirms the human origin of the orthotopic human PanIN-like and PDA cells. Scale bars represent 50  $\mu$ m.

## 5. Research Strategy and Methods

We include in this section a review of our history and rationale for the proposed partnership for pilot research project P2.

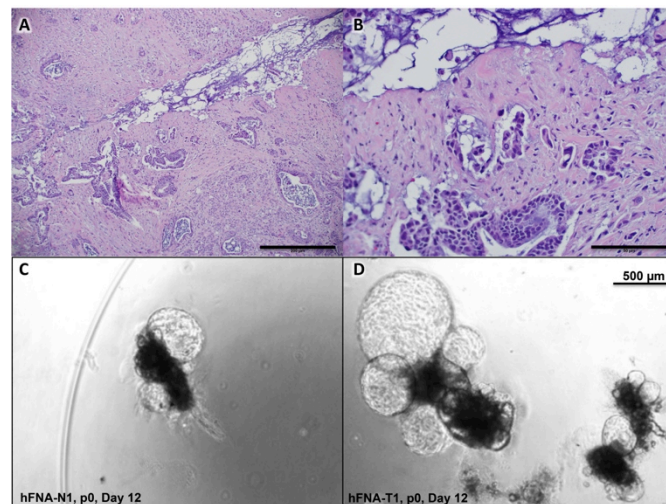
### 5A. History of Developing the SUNY-CSHL Partnership to Study Racial/Ethnic Differences in Pancreatic Cancer Biology

To promote collaborations between the SUNY Stony Brook Cancer Center and the NCI-designated Cancer Center at CSHL on pancreatic cancer, a Long Island Pancreatic Cancer meeting was organized and held on January 10, 2014 at CSHL. At this meeting, members of Dr. Tuveson's laboratory presented their results on developing pancreatic organoids from mouse models of pancreatic cancers, and discussed the possibility of using these models for testing sensitivity to various chemotherapeutic agents. The SUNY Stony Brook interventional endoscopists, including **Dr. Bucobo**, who attended this meeting became very excited about the possibility about applying this technology to test chemotherapy reagents on human models of pancreatic cancers derived from endoscopic ultrasound guided fine needle core biopsies (EUS-FNB) of pancreatic cancers that were inoperable. They foresaw that developing this model could potentially lead to the development of a more personalized approach to the treatment of inoperable pancreatic cancers. **Dr. Martello Rooney** who also attended this meeting, was also very interested in adapting this technology at SUNY Downstate. From that meeting **Dr. Li** made a commitment to begin the collection process by the SUNY Stony



**Figure 5.** Targeted sequencing analysis of human organoids. Genes altered in more than one sample and/or known to be mutated in PDA are shown. If multiple mutations were found in a gene, only one mutation per gene is shown. Color key for the type of genetic alterations is shown. Met indicates organoids derived from metastatic samples.

Brook GI Biobank to generate preliminary data in support of future applications for extramural support so that parallel collection efforts could be initiated at SUNY Downstate. Initially ex-vivo FNBs were obtained on freshly resected pancreatic cancer specimens. SUNY Stony Brook Cancer Center and subsequently Stony Brook IRB approval for the in-vivo EUS FNB research biopsies was obtained January 2015, 7 months after submission of the original P2 application and the original IRB application were submitted in May 2014. The first in vivo EUS-FNB research sample sent to CSHL within 2 hours of the procedure resulted in successful generation of pancreatic organoids. We are currently in the process of obtaining IRB approval at SUNY Downstate, but this process should be facilitated by the fact that Dr. Martello-Rooney has already obtained IRB approval for generating conventional pancreatic cell lines from EUS-FNB. The inclusion of **Dr. Vignesh**, who joined SUNY Downstate as the new Chief of Gastroenterology in October 2014, will promote the collection of EUS-FNB from URM patients using the protocols developed between SUNY Stony brook and CSHL over the past 8 months.



**Figure 6:** **A:** H&E showing the needle track from the FNA biopsy of the resected primary tumor. Scale bar = 200μm. **B:** Higher magnification of the needle track showing the proximity to tumor cells. Scale bar = 50μm. **C&D:** Brightfield images of human organoids established from FNAs of normal (C) or tumor tissue (D) 12 days after isolation.

### 5B1. Aim 1. Preparation of URM pancreatic cancer organoids.

The protocol for recruiting patients at SUNY Downstate will be identical to the current protocol for recruiting patients at SUNY Stony Brook. Patients undergoing planned EUS-FNB procedures (as clinically indicated) for the diagnosis of a pancreatic mass suspicious for PDA will be asked to consider participation in the research study at the time the procedure is scheduled. All EUS-FNB procedures will be performed by a member of the SUNY Downstate University Interventional Endoscopy Section of the Division of Gastroenterology and Hepatology (under **Dr. Vignesh**). The inclusion criteria are age ( $\geq 18$ ), as well as ability and willingness to consent to providing specimens for propagation of cell lines and use of research materials for genetic work. Furthermore, patients consent to the collection of EDTA blood tubes (~15 -20 ml), and to the collection of longitudinal clinical data. The exclusion criteria include patient previously treated with chemotherapy or radiation, age ( $< 18$ ), and unable to provide informed consent. The EUS-FNB will be performed using a 22G FNB needle with an on-site cytopathology technician in the procedure room. Since the risks of complication associated with FNA/FNB are believed to be increased with  $> 7$  needle passes (using standard needle sizes of 22G and 25G) [44-46] only those patients in which adequate cellular material is achieved in  $\leq 5$  passes will be permitted to continue their participation in the study. After adequate sample is obtained upon assessment by the cytopathology technician, two additional needle passes will be performed for the research purposes. The FNB specimens will be placed into basal organoid media, and will be transported to the Stony Brook GI Biobank (HSC17-080) immediately (within 2 h) for delivery to **Dr. Tuveson's** laboratory at CSHL for further processing to generate organoids.

**Dr. Martello-Rooney** will collect paired ex-vivo FNB and cross-sectional samples in collaboration with the pancreatic surgeons at Kings Hospital and SUNY Downstate following the same protocol currently used at the SUNY Stony Brook GI Biobank. The inclusion and exclusion criteria will be the same between all institutions. Research samples will be obtained from the surgical waste only after the attending pathologist makes a decision as to whether there is sufficient tumor left over after the sample required for diagnosis is secured. In addition to the ex-vivo FNB and parallel  $1\text{cm}^3$  cross-sectional specimens transported to the **Tuveson** laboratory. The remaining surgical waste will be archived as frozen tissue within the SUNY Downstate GI Biobank.

Pancreatic organoids generated in **Dr. Tuveson's** laboratory from freshly surgically resected specimens will be processed after transport as previously described [18]. We applied an adapted procedure to process FNB samples of pancreatic tissues. This procedure utilizes reduced digestion periods to maximize viability while sufficiently fragmenting the tissue. Furthermore, we have enriched our methodology to limit cell loss during washes by optimizing recovery conditions in low protein-binding plastic-ware. Finally, we plated the

tissue fragments in just a few Matrigel-domes in the presence of our defined, mitogen-rich media. We have successfully adapted the procedure to grow organoids from ex-vivo and in-vivo FNB samples obtained through the SUNY Stony Brook GI Biobank within 12 days of receiving the sample (**Fig. 6**). Based on these preliminary results we are reasonably confident that organoids can be grown from a single FNB pass and are ready to apply this protocol to a larger cohort of patients. We plan to generate pancreatic organoids from 10 URM patients/year for a total of 40 URM patients over the 4 year duration of this award. SUNY Stony Brook will plan to generate a further 10 non-URM patients/year for a total of 40 non-URM patients and is currently seeking other funding sources to support this effort.

*Expected results and future plans.* We will determine the efficiency with which pancreatic tumor organoids can be derived from in vivo EUS-FNB samples, ex-vivo EUS samples and ex-vivo cross-sectional samples at SUNY Downstate as they develop their GI Biobank infrastructure. Our aim is to achieve comparable high (80-90%) efficiency at both SUNY GI Biobanks. It may be that some of the surgically resected specimens are too small for the attending surgical pathologist to allow reserving a 1 cm<sup>3</sup> sample for transport to CSHL, and the amount of resected pancreatic tumor transported may be smaller. Based on our preliminary results using SUNY Stony Brook samples we are reasonably confident about the feasibility of generating pancreatic organoids from EUS-FNB samples. To ensure a smooth transfer of protocol, **Dr. Bucobo** and members of the SUNY Stony Brook GI Biobank (e.g. technician/runner) will be present for the initial set of EUS-FNB and surgical resection patients collected at SUNY Downstate. Our plan will be to use the preliminary data generated in this P20 award to apply for larger research awards to support an expansion of the number of patients that can be processed for organoid generation.

## **5B2. Aim 2: Molecular characterization of URM pancreatic cancer organoids**

Following the establishment of organoids from 40 URM patients, we will perform gene expression analysis as well as genomic profiling in collaboration with the McCombie laboratory and compare these organoids to 40 previously established non-URM patient-derived organoids. To better understand the cellular pathways deregulated in human pancreatic cancer cells and to determine how these pathways differ between URM and non-Hispanic White American populations, we plan to use RNA-sequencing (RNA-seq) to define the genes whose expression levels differ between normal and tumor human organoids. RNA will be isolated from tumor organoid lines and any matched normal organoid lines. RNA quality will be assessed using an Agilent Bioanalyzer, and only RNA samples with RIN values greater than 9.0 will be used for sequencing. Ribosomal RNA will be depleted from the RNA samples, and the remaining RNA will be used to generate stranded RNA-seq libraries using an Illumina TruSeq kit. Libraries will be assessed by Bioanalyzer and sequenced at the Cold Spring Harbor Laboratory DNA Sequencing Shared Resource using an Illumina HiSeq 2000 instrument. Up to 3 RNA-seq libraries will be pooled per flow-cell lane to ensure adequate sequence coverage for expression analysis. Sequencing data will be analyzed with help from the Cold Spring Harbor Laboratory Bioinformatics Shared Resource. Data will be aligned to the human genome and transcript abundance will be called using the RSEM program [47]. Differentially expressed genes will be identified using the DeSeq program [48]. Pathway analysis programs such as Gene Set Enrichment Analysis (GSEA) [49] and The Database for Annotation, Visualization and Integrated Discovery (DAVID) [50] will be used to identify biological pathways deregulated in human tumor organoids.

Previous studies looking at RNA-sequencing have estimated that 30-40 million sequencing reads are sufficient “to be technically precise in measuring gene expression for most genes” [51, 52]. Therefore, for our RNA-sequencing experiments we plan to pool 3 samples per sequencing lane. Since a typical sequencing lane at the laboratory’s Next Generation Sequencing Shared Resource yields approximately 200 million reads, this should ensure adequate sequence coverage. A power analysis was done using a calculation designed for RNA-sequencing experiments [51] to determine the feasibility of our RNA-sequencing experiments. Assuming that we will average 40 reads per gene and will have a coefficient of variation around 0.5 (estimated from a previous RNA-sequencing experiment done in the laboratory), using an alpha of 0.05 and a power of 90%, using 40 samples per group (URM vs. non-URM) will allow us to reliably measure genes with a fold-change 2.1 or greater.

Expression changes identified in our dataset will be confirmed using qRT-PCR analysis, and changes will also be confirmed at the protein level by immunohistochemistry following organoid transplantation in Aim 3. The pathways found to be enriched in URM patients will be compared to expression analyses of Non-Hispanic White American populations to distinguish differential corruption of biological processes.

We will also perform whole exome sequencing of the samples using the Illumina HiSeq technology in collaboration with the McCombie laboratory. Normal reference DNA from each URM patient will be obtained from white blood cells. The resulting sequencing data will be compared to the ICGC pancreas cancer mutation dataset and will be used to identify and rank the somatic mutations present in our organoids. The ICGC dataset largely reflects Australian patients of Non-Hispanic White descent, and our work will be the first specifically probing the pancreatic cancer genome in URMs. We will also compare the URM-related mutational profile to that of non-URM organoids. Finally, we will validate the top mutations using an orthogonal sequencing approach such as ion torrent technology. We will carefully evaluate potential new drivers of pancreatic cancer in these URM patients and identify over-represented pathways.

Expected Results/Future Plans: We will use the data obtained from the next generation sequencing to correlate genetic and gene-expression signatures with the patient outcome and race. Initially, we will compare the mutations identified in URMs to existing databases predominantly obtained from Non-Hispanic Caucasian populations to identify any genetic changes that are more or less prevalent in URMs. To interrogate possible impact on patient survival, we will correlate both gene expression analysis and genomic profiling to patient outcome.

To accomplish this, we will share our data with all the SUNY and CSHL groups involved in this work. Tumor burden, metastases, and therapeutic response will be evaluated in relation to the somatic mutations present in each patient. Furthermore, the gene expression analysis will provide another layer of information about the tumor that can be used to better characterize these URM patients.

Given that these organoids are amenable to genetic manipulation through viral transduction or CRISPR/Cas9-mediated gene editing, these studies will enable iterative cycles of discovery and validation for future studies of genetic drivers of pancreatic cancer in under represented minorities.

Pitfalls/Alternatives: The ICGC was generated from resected primary pancreatic cancers, and thus a comparison to primary tumors from patients with advanced pancreatic cancer may be imprecise. In this case, we can restrict our analysis between URM organoid samples from patients of a certain disease stage (resectable, locally advanced, or metastatic), and non-URM samples from patients of the same disease stage.

### **5B3. Aim 3: Tumor progression studies of URM pancreatic cancer organoids**

We have previously demonstrated that human pancreatic tumor organoids derived from surgical resection specimens initially develop into early-stage PanIN lesions when orthotopically transplanted progressed to PDA over several months [18] (**Figure 3** and **Figure 4**). These transplanted human tumor organoids also induce a robust desmoplastic reaction, as evidenced by deposition of ECM components and presence of stromal cells (**Figure 4**). Thus, this organoid culture system recapitulates the multiple steps of PanIN and PDA progression upon orthotopic transplantation.

To determine if cellular behavior differs between URM and non-URM PDA, URM and non-URM pancreatic cancer organoids, from the same disease stage, will be orthotopically transplanted into immunodeficient mice at Dr. Mackenzie's laboratory [53], and tumor progression monitored by sacrificing cohorts of animals at various stages of disease progression until animals succumb from disease. In this pilot study, organoids representing both primary resectable and metastatic PDA will be used for this evaluation (N=4 total). Cohorts of 6 mice each will be sacrificed after 1 month and 4 months to represent early and advanced disease states. The speed of progression of preinvasive to invasive and metastatic PDA will be assessed, as well as the recruitment of the tumor microenvironment (*see letter of support from our board-certified Pathologist Dr. Ken Shroyer*). Furthermore, since URM pancreatic cancers were previously described to have increased local invasion at the time of surgery [21], this feature will also be assessed in resected specimens. Cellular proliferation and the activation of characteristic signaling pathways (MAPK, EGFR, PI3K) will also be assessed. This in vivo phenotypic assay will be used to complement the molecular approaches of Aim 2.

Expected Results/Future Plans: We anticipate that orthotopically transplanted URM organoids will demonstrate a different pattern of neoplastic progression when compared to non-URM organoids. If this is the case, the pathways responsible for differences in progression will be sought. Such pathways will represent potential therapeutic targets for PDA in URMs.

Pitfalls/Alternatives: If there is no difference in behavior when transplanted into NSG (NOD-SCID-gamma), we will also assess in the obese mouse background, since this may be the environmental trigger for URM increased pancreatic cancer risk.

## **Protection of Human Subjects**

As part of this proposal, human three-dimensional organoids, will be generated from normal human pancreatic tissue or human pancreatic ductal adenocarcinomas. Human normal pancreatic tissue will be obtained from de-identified human autopsy samples used to isolate material for pancreatic islet transplantation. Because this tissue comes from deceased humans, these samples do not meet the criteria for human subject research according to federal regulations. Nonetheless, we have approval through the Cold Spring Harbor Laboratory IRB under the project title "[556949-1] Isolation and analysis of normal pancreatic exocrine tissue," and a copy of this approval letter is included in the Appendix of this proposal.

Fine needle aspirate from human pancreatic adenocarcinoma specimens will be obtained from de-identified patients. We have approval for this through the Cold Spring Harbor Laboratory IRB, under the project title [588966-1] "Collection of Tissue, Blood and Other Specimens from Patients [Stony Brook Medicine]" and a copy of this approval letter is included in the Appendix of this proposal. Because all samples we receive will be de-identified, the Cold Spring Harbor Laboratory IRB has unanimously agreed that the proposed research qualifies for an exemption under 45 CFR 46.101 (b) (4).

## **Inclusion of Women and Minorities**

For pancreatic cells isolated from human autopsy samples, de-identified samples will be collected from deceased males and females of any ethnic group as they are available and meet the criteria for human islet cell transplant. Only after pancreatic islet cells suitable for transplant have been removed from these samples do we receive them.

For pancreatic tumor specimens taken from living patients, de-identified tumor tissue will be obtained from patients being treated for pancreatic ductal adenocarcinoma at SUNY medical institutions. Our study will aim to collect samples from males and females of under represented minorities to serve as the material for this study.

## Planned Enrollment Report

**Study Title:** Pilot 2: Organoids to investigate Pancreatic Cancer in under represented minorities

**Domestic/Foreign:** Domestic

**Comments:**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	20	20	0	0	40
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	20	20	0	0	40

Study 1 of 1

## **Inclusion of Children**

Pancreatic ductal adenocarcinomas are almost never found in children so no children will be used in this study.

## PILOT RESEARCH PROJECT P2 -VERTEBRATE ANIMALS

### 1. **Proposed use of animals**

We will use mice as described in the Pilot Research Project Research Strategy section. Animal numbers and their planned use in Pilot Project 2 are listed below.

#### **Specific Aim #1: Preparation of URM pancreatic cancer organoids**

- No animals needed

#### **Specific Aim #2: Molecular characterization of URM pancreatic cancer organoids**

- No animals needed

#### **Specific Aim #3: Tumor progression studies of URM pancreatic cancer organoids**

- *Orthotopic tumor (T) organoid implants [See below a)]*:
  - Four independent experiments: female SCID mice 5-6 wks old
  - Two groups per experiment: a) URM; b) Non-URM (same disease stage).
  - Two time-points: 1-month post implantation and 4-month post implantation.
  - Six animals per group per time-point

Total = **96 mice** (for all four independent experiments)

### **Detail description of the proposed studies**

#### **a) Orthotopic implantation of pancreatic T organoids**

SCID mice represent a widely used animal model for such purposes. These mice have no immune reaction to human cells or tumors when they are implanted in them (ordinary mice reject them). This animal model provides the opportunity to assess the tumor progression studies in URM and Non-URM pancreatic cancer organoids.

### **Experimental procedures**

#### **Implantation of URM and Non-URM tumor organoids into SCID mice**

1. For the orthotopic engraftment of human T organoids, mice are anesthetized using Isoflurane (5% induction, 2% maintenance), and Ketrolac (5 mg/kg), subcutaneously administered.
2. An incision is made in the left abdominal side.
3. URM and Non-URM organoids ( $1 \times 10^6$  cells/mouse) are prepared either from cultures or from cryopreserved stocks. In the case of cryopreserved stocks, organoids are thawed in HEPES (1x, Invitrogen), Glutamax (1x, Invitrogen), and penicillin/streptomycin (1x, Invitrogen), in AdDMEM/F12 media and stabilized for 4 hr at 37°C in 5% CO<sub>2</sub>. Organoids are washed with ice-cold PBS, physically broken into pieces by triturating through fire-polished glass Pasteur pipettes, and finally resuspended in 50 µl of Matrigel (Matrigel, BD) diluted 1:1 with cold PBS.
4. The organoid suspension is injected into the tail region of the pancreas using insulin syringes (29 Gauge). Successful injection is verified by the appearance of a fluid bubble without signs of intraperitoneal leakage.
5. The abdominal wall is then sutured with absorbable Vicryl suture (Ethicon), and the skin is closed with wound clips (CellPoint Scientific Inc.).
6. Mice are euthanized at the indicated time points (one month and four-month implantation).

### **Anesthesia**

**Agent:** Isoflurane: 5% for induction; and then 2% for the maintenance during the procedure

After surgery, The animals will be monitored on the heating pad until they begin to move. Once movement is observed, usually 30 to 45 minutes later, the animals will be placed in their original sterile isolation cages. Before departing for the day, the animals will be observed once more to ensure that no problems arose.

*Monitoring parameters and frequency:* Observation until the animals are awake and moving around.

*How recovery monitoring will be performed:* Visual observation.

### Analgesia

Topical lidocaine will be provided immediately post-op. All animals will receive one dose of Ketorolac 5 mg/kg SQ. If they continue showing signs of pain, we will continue administering Ketorolac until pain ceases.

Animals will be checked to monitor for the presence of pain, discomfort or distress until they are awake and moving around. After that, we will observe the animals visually daily.

## **2. Justification of use of animals:**

There are two key advantages in using human T organoid models for tumor progression studies: **1)** T organoids can propagate rapidly, operating on a time scale of weeks instead of the years, as it takes to establish patient derived xenografts; and **2)** Tumor organoids develop a surrounding desmoplastic reaction, better mimicking what occurs in human PDA. This is in contrast to what is observed in two-dimensional human PDA cell lines, which lack of stromal reaction. We propose to use URM and non-URM pancreatic cancer organoids orthotopically transplanted into immunodeficient mice (SCID mice), to determine if cellular behavior differs between URM and non-URM PDA.

Statistical power calculations: With 6 animals or tumors per group per time-point, we have 82% power to detect a 34% difference in tumor growth between URM and NON-URM assuming a 1-tailed alpha=0.05 t-test. Statistical Analysis: Tumor weight will be compared among the experimental groups using one-way ANOVA followed by Tukey's method of multiple comparisons.

## **3. Veterinary care of the animals:**

Animals are housed in one of our state-of-the-art Animal Facilities at Stony Brook University. The Division of Laboratory Animal Services (DLAR) at Stony Brook University is administratively centralized but the services are campus-wide. The main facility is on the ground level of the Health Sciences Center. This is a 36,500 sq. ft. facility that provides the administrative space for the DLAR, diagnostic laboratory, necropsy, X-ray unit, gamma camera, a teaching surgery room used primarily for non-survival procedures, a section of four large modern survival surgery suites with adjacent locker change rooms, scrub room pre-op and post-op rooms. There are two autoclaves in the surgery area and four in another location. Gas sterilization is provided by central sterilizing. The facility has housing suitable for most any species one would need to use.

The DLAR is staffed with people of appropriate education and experience. There is seven day per week animal care with two veterinarians rotating after hours, weekend and holiday call. The trainings required by the Office for Protection from Research Risks (OPRR) and the Animal Welfare Act are provided by the Director of the DLAR and his assistants. The University Assurance statement to OPRR has been accepted and the IACUC is duly constituted and meets every two weeks. The DLAR is fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). All experimental protocols are submitted to IACUC for approval. A detailed description of justification of the use of animals, the choice of species, and the number of animals to be used is given in "Experimental Procedures." A fully equipped diet laboratory and low temperature storage facility for pre-mixed diets are available. Animals are cared for seven days a week every day of the year. All animals are quarantined for 10 days prior to their transfer to a holding room. During this time, they are carefully screened for internal and external parasites, respiratory and fecal pathogens, blood parasites, dermatophytes and viruses. A selected population is necropsied and a histopathological study performed. All animals will be maintained under controlled conditions (21°C and 50% relative humidity in a 12h-light/dark cycle). They will be fed *ad libitum* with free access to water.

All animals are examined at least twice daily. Weights are recorded once weekly and any untoward findings are reported to the veterinarian in charge.

## **4. Procedures ensuring comfort of animals:**

During the surgical procedures described above, the animals will suffer discomfort. To minimize the discomfort, we will anesthetize the mice (please see above for details). Furthermore, animals will be checked

twice daily to monitor for the presence of pain, discomfort or distress after the surgery. They will receive analgesia for this purpose (ketorolac and lidocaine). Any animal that continues showing signs of pain, will be administered with extra analgesia as needed. Moreover, we will check for potential signs of infection in the surgical implant site. If we observe any signs of infection, the animals will be treated with antibiotics. If we observe any signs of suffering, we will euthanize the sick animals.

### ***5. Methods of euthanasia***

CO<sub>2</sub> euthanasia will be used and it has been selected for its simplicity and comfort to the animals. The method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. Following euthanasia with CO<sub>2</sub>, we will perform cervical dislocation to ensure death of the animals.

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*School of Medicine  
Division of Gastroenterology and Hepatology*

Dr. Gerardo Mackenzie  
Assistant Professor of Preventive Medicine  
Stony Brook Medicine

RE: Feasibility Studies to Build Collaborative Partners in Cancer Research

Dear Gerardo,

I am writing to confirm my role as a co-investigator in pilot project P2 in the section of your planning grant application entitled "Partnership to study racial/ethnic differences in GI cancer biology" in GI cancer biology" in response to PAR-14-152 "Feasibility studies to Build Collaborative Partners in Cancer Research".

This pilot project clearly demonstrates our commitment as a faculty in Stony Brook Medicine's Division of Gastroenterology and specifically the Interventional Endoscopy group in utilizing the most advanced endoscopic technique to offer the highest level of patient care and research. This groundbreaking research project is especially important to me as it provides us the opportunity to join forces with the renowned Dr. David Tuveson and his lab at Cold Spring Harbor Laboratories in developing pancreatic cancer organoids from specimens we will obtain by endoscopic ultrasound. This will allow us to create a living biobank of both unresectable and resectable pancreatic cancers and may represent an important technological advance for Precision Medicine. This translational research project truly exemplifies the concept of bringing science from the "bench to the bedside".

You can count on my support as a co-investigator in this study by providing my expertise as an interventional endoscopist and clinical researcher. This study has tremendous potential in impacting future patient care and I wish you success in this proposal. I look forward to this collaboration with you and the entire pancreatic organoid team.

Sincerely,

A handwritten signature in black ink, appearing to read "J. Bucobo".

Juan Carlos Bucobo, MD  
Director of Endoscopy  
Assistant Professor of Medicine  
Division of Gastroenterology and Hepatology  
Stony Brook Medicine  
Tel: (631) 444-2119, Fax: (631) 444-8886  
juancarlos.bucobo@stonybrookmedicine.edu



March 18, 2015

Dr. Ellen Li  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

RE: Feasibility studies to Build Collaborative Partners in Cancer Research

Dear Dr. Li (Ellen) –

I am delighted to write this letter to express my willingness to serve as the SUNY contact PI for Pilot Project P2 on pancreatic organoids for the Cancer Research Program of your planning grant application entitled "Partnership to study racial/ethnic differences in GI cancer biology" in response to PAR-14-152 "Feasibility studies to Build Collaborative Partners in Cancer Research".

Working closely with Dr. David Tuveson and his laboratory at CSHL, I will lead the SUNY Stony Brook effort in the tumor progression studies of URM pancreatic cancer organoid, to explore whether there are innate cell biological differences between URM and non-URM pancreatic cancer cells. For this purpose, URM pancreatic cancer organoids will be transplanted orthotopically and tumor progression will be compared to non-URM samples. I have a broad background in preclinical models of pancreatic cancer, with specific training and expertise in key research areas for this application, such as orthotopic models of PDA. We expect that the tumor progression studies will assist us with determining whether there are particular genetic contexts and signaling pathways that are different in URM pancreatic cancer compared to non-URM pancreatic cancer. They will provide another layer of information about the tumor that can be used to better characterize these URM patients. In summary, my expertise and vast experience in animal tumor models, mechanistic studies, and my record of accomplished and productive research projects in an area of highly relevance for our population, have prepared me to co-lead the proposed pilot project.

Sincerely

A handwritten signature in blue ink, appearing to read "Gerardo Mackenzie".

Gerardo Mackenzie, Ph.D.  
Assistant Professor of Preventive Medicine

Stony Brook University Hospital  
Department of Preventive Medicine  
Health Science Tower  
101 Nicolls Road  
Level 17 Room 080  
Stony Brook, New York 11794-8173  
P: 631-444-2119 F: 631-444-8886



SUNY  
**DOWNSTATE**  
Medical Center

University Hospital of Brooklyn  
College of Medicine  
School of Graduate Studies  
College of Nursing  
College of Health Related Professions

Department of Medicine  
Division of Gastroenterology & Hepatology

March 11, 2015

Ellen Li, MD, PhD  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

Dear Dr. Li:

This letter confirms my commitment as a Co-Investigator for the study entitled “Feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research” proposed in this application and submitted in response to the NIH/NCI P20 Funding Opportunity for “Feasibility Studies to Build Collaborative Partnerships in Cancer Research”. My involvement relates to oversight of the Pilot Projects at the SUNY Downstate campus in addition to the training of students. As PI of the SUNY Downstate IRB for miRNA analysis of colon cancer samples, I have been coordinating with the Department of Pathology the retrieval and transfer of colon tumor fixed tissue sections to SUNY Stony Brook for testing and this will be extended to colon tumor fresh tissues for the development of colon cancer cell lines. I also have been working closely with Drs. Vignesh and Grossman, in the GI Division, who will be providing fine-needle biopsy pancreatic tumor specimens from African American patients for the generation of pancreatic organoids.

As Director of GI Research, I have been involved in the initiation of various translational research projects focused on pancreatic cancer. These projects have included as participants GI Fellows, Internal Medicine Residents as well as Medical and Graduate students. I welcome the opportunity to expand the project opportunities as a continued way to expose them to the value of research especially as it relates to cancer health disparities.

Sincerely,

A handwritten signature in cursive script that reads 'Laura Martello-Rooney'.

Laura Martello-Rooney, PhD  
Director of GI Research  
Research Assistant Professor of Medicine  
Division of Gastroenterology & Hepatology  
SUNY Downstate Medical Center  
450 Clarkson Ave, MSC 1196

**State University of New York Downstate Medical Center**

450 Clarkson Avenue, MSC 1196, Brooklyn, NY 11203-2098 • Phone 718 270 - 1113 Fax 718 270 - 7201

Brooklyn, NY 11203

Ph: 718-270-1290

[laura.martello-rooney@downstate.edu](mailto:laura.martello-rooney@downstate.edu)



SUNY  
**DOWNSTATE**  
Medical Center

University Hospital of Brooklyn  
College of Medicine  
School of Graduate Studies  
College of Nursing  
College of Health Related Professions

Department of Medicine  
Division of Gastroenterology & Hepatology

March 10, 2015

Ellen Li, MD, PhD  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

Dear Dr. Li:

This letter confirms my commitment as a Co-Investigator for the study entitled "Feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research" proposed in this application and submitted in response to the NIH/NCI P20 Funding Opportunity for "Feasibility Studies to Build Collaborative Partnerships in Cancer Research". My involvement relates to Pilot Project 2 and the collection of fine-needle biopsy samples for generation of pancreatic organoids. In addition, I will facilitate the coordination samples collection from the different departments, including Surgery, Oncology and Pathology with the help of the appropriate staff.

As the new Chief of Gastroenterology recently recruited from Moffitt Cancer Center, I welcome the opportunity to be involved in projects of this nature. I've been trained as an interventional endoscopist and specialized in Endoscopic Oncology for the last six years. I have prior experience conducting GI cancer trials and coordinating sample acquisition and storage, and will coordinate similar efforts at Downstate including patient recruitment and facilitating assistance of related services. I also will be working closely with Dr. Martello-Rooney to build the infrastructure for the Downstate GI Cancer Biobank.

Sincerely,

A handwritten signature in dark ink, appearing to read "Shivakumar Vignesh".

Shivakumar Vignesh, MD  
Chief, Division of Gastroenterology & Hepatology  
Department of Medicine  
SUNY Downstate Medical Center  
450 Clarkson Ave, MSC 1196  
Brooklyn, NY 11203  
Ph: 718-270-1113  
[shivakumar.vignesh@downstate.edu](mailto:shivakumar.vignesh@downstate.edu)

**State University of New York Downstate Medical Center**

## Resource Sharing Plan: Pilot Project P2

We will follow relevant NIH guidelines for data sharing. In accordance with NIH Resource Sharing Policy and the NIH Genomic Data Sharing Policy effective January 25, 2015, the investigators will share data and resources at the earliest opportunities throughout this research, subject to patient privacy concerns. Following careful curation of sequence data and clinical metadata, the Steering Committee will review the release of those data to the appropriate NCBI databases (dbGAP, Short Read Archive or SRA). Tables on cohort subject and sample metadata will be deposited in dbGAP, which is a controlled access database. We anticipate that the data generated by the team will be made available as somatic variant data and can therefore be placed on publicly accessible repositories. In addition, results will be written up and sent for publication in relevant journals and the investigators will seek to present publishable results at scientific conferences worldwide.

## APPLICATION FOR FEDERAL ASSISTANCE

**SF 424 (R&R)****5. APPLICANT INFORMATION****Organizational DUNS\*:** 8048782470000

Legal Name\*: The Research Foundation for SUNY, Stony Brook University  
 Department: Office of Sponsored Programs  
 Division: OVPR  
 Street1\*: STONY BROOK UNIVERSITY  
 Street2: The Office of Sponsered Programs  
 City\*: STONY BROOK  
 County:  
 State\*: NY: New York  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 117940000

Person to be contacted on matters involving this application

Prefix: First Name\*: Middle Name: Last Name\*: Suffix:  
 Ms. Andria  
 Position/Title: Grant Administrator  
 Street1\*: W5510 Melville Library  
 Street2: Stony Brook University  
 City\*: Stony Brook  
 County: Suffolk  
 State\*: NY: New York  
 Province:  
 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 117943362  
 Phone Number\*: 631 632-1610 Fax Number: 631 632-6963 Email: andria.adler@stonybrook.edu

**7. TYPE OF APPLICANT\***

X: Other (specify)

Other (Specify): Non Profit

**Small Business Organization Type**☐ Women Owned☐ Socially and Economically Disadvantaged**11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT\***

Training and Education Program

**12. PROPOSED PROJECT**

Start Date\* Ending Date\*  
 09/01/2015 08/31/2019

**Project/Performance Site Location(s)****Project/Performance Site Primary Location**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY, Stony Brook University  
Duns Number: 8048782470000  
Street1\*: STONY BROOK UNIVERSITY  
Street2: The Office of Sponsered Programs  
City\*: STONY BROOK  
County:  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 117940000  
Project/Performance Site Congressional District\*: NY-001

---

**Project/Performance Site Location 1**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Research Foundation for SUNY - Downstate Medical Center  
DUNS Number: 0407963280000  
Street1\*: 450 Clarkson Avenue  
Street2:  
City\*: Brooklyn  
County: Kings  
State\*: NY: New York  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 112030000  
Project/Performance Site Congressional District\*: NY-011

---

File Name

**Additional Location(s)**

## RESEARCH &amp; RELATED Other Project Information

<b>1. Are Human Subjects Involved?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
1.a. If YES to Human Subjects Is the Project Exempt from Federal regulations? <input type="radio"/> Yes <input type="radio"/> No If YES, check appropriate exemption number:      — 1 — 2 — 3 — 4 — 5 — 6 If NO, is the IRB review Pending? <input type="radio"/> Yes <input type="radio"/> No IRB Approval Date: Human Subject Assurance Number	
<b>2. Are Vertebrate Animals Used?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
2.a. If YES to Vertebrate Animals Is the IACUC review Pending? <input type="radio"/> Yes <input type="radio"/> No IACUC Approval Date: Animal Welfare Assurance Number	
<b>3. Is proprietary/privileged information included in the application?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
<b>4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
4.b. If yes, please explain: 4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? <input type="radio"/> Yes <input type="radio"/> No 4.d. If yes, please explain:	
<b>5. Is the research performance site designated, or eligible to be designated, as a historic place?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
5.a. If yes, please explain:	
<b>6. Does this project involve activities outside the United States or partnership with international collaborators?*</b> <input type="radio"/> Yes <input checked="" type="radio"/> No	
6.a. If yes, identify countries: 6.b. Optional Explanation:	
<b>7. Project Summary/Abstract*</b>	Filename P20abstract031915.pdf
<b>8. Project Narrative*</b>	Narrative.pdf
<b>9. Bibliography &amp; References Cited</b>	Refs_Training.pdf
<b>10. Facilities &amp; Other Resources</b>	
<b>11. Equipment</b>	
<b>12. Other Attachments</b>	Biosketch_Binder1_B.pdf

## ABSTRACT

Two SUNY medical campuses (SUNY Stony Brook and SUNY Downstate) serving underrepresented minority communities with cancer health disparities are partnering with the NCI designated Cancer Center at the Cold Spring Harbor Laboratories to evaluate biological and genetic differences in GI cancers (colorectal and pancreatic) that may link to differences in cancer incidence and outcome observed in racial and ethnic minorities (URM). For the Cancer Research Program, we aim to augment the representation of underrepresented minorities in the collection of biospecimens and linked high dimensional 'omic datasets generated from these biospecimens. In this planning grant we plan to develop a SUNY Downstate GI Biobank that operates in parallel to the SUNY Stony Brook GI BioBank using standard operating procedures. We are planning the development of an integrative biomedical informatics platform that will link the biospecimens with longitudinal clinical data and with the data generated from these specimens. An initial step in the planning procedure is to develop a consensus of what data elements to include and for developing a controlled vocabulary. To increase community participatory research among racial and ethnic minority populations, we plan to leverage the resources and expertise of the SUNY Downstate Brooklyn Health Disparities Center (led by Dr. Moro Salifu) in developing community education and outreach programs in underserved communities with a high proportion of racial and ethnic minorities. The collection of biospecimens will be driven by two pilot research projects, P1 and P2. In P1, we propose to compare genomic and epigenetic profiling of URM colon cancers with non URM colon cancers. In P2, we propose to test the feasibility of adapting an innovative 3-D method to grow pancreatic organoids (miniature pancreas) from progenitor cells (developed in Dr. Tuveson's laboratory at CSHL) from fine needle core biopsies of human pancreatic cancers collected at the two SUNY medical campuses. We plan to compare genomic and epigenomic profiling of URM pancreatic organoids with those of non-URM organoids. For the Training and Education Program, we are committed to improving the participation of underrepresented minorities in biomedical research and in increasing awareness of health disparities among established cancer researchers. In this planning grant the two SUNY medical campuses will partner with CSHL to create an integrated doctoral certificate program Scholars in BioMedical Sciences in Cancer Health Disparities. This program is designed to engage doctoral students in translational medicine, particularly in cancer health disparities, by promoting in these students an understanding of the presentation, progression and treatment of diseases related to their area of thesis research. The track requires the addition of a clinical co-mentor to the usual student-basic science advisor team who will help guide the student's biomedical/clinical research and immerse the student in clinical experiences, vocabulary, and the overall culture of clinical research.

## **Narrative**

This training and education program seeks to enhance diversity in the cancer research workspace. This will be achieved by integrating knowledge on the role of population diversity in cancer related health disparities and patient outcomes among graduate students from under represented communities and their faculty mentor.

Program Director/Principal Investigator (Last, First, Middle): CARETHERS, John M.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>JOHN M. CARETHERS, M.D.</b>	POSITION TITLE John G. Searle Professor of Internal Medicine Chair, Department of Internal Medicine		
eRA COMMONS USER NAME (credential, e.g., agency login) jcarethers			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Wayne State University	B.S.	1981-1985	Biological Sciences
Wayne State University	M.D.	1985-1989	Medicine
Massachusetts General Hospital	Residency	1989-1992	Internal Medicine
University of Michigan Hospitals	Fellowship	1992-1995	Gastroenterology

**A. Personal Statement**

I have >20 years experience in the field of colorectal cancer and genetics within gastroenterology, and know the importance of training the next generation of physician-scientists, with experience as a T32 director, fellowship director, division chief and department chair, coupled with the more than 50 trainees I have mentored. I have a vested interest in the field of cancer disparities, with experience as PI (current U01) and former co-PI of a U54 Comprehensive Cancer Center Partnership, Program Leader of the Reducing Cancer Disparities program at a comprehensive cancer center, and multiple publications regarding the approach to care and the biology of colorectal cancer among African Americans.

**B. Positions, Employment, and Honors**

1995-2001 Assistant Professor of Medicine in Residence, University of California, San Diego  
 2000-2004 Gastroenterology Fellowship Director, University of California, San Diego  
 2001-2005 Associate Professor of Medicine, University of California, San Diego  
 2002-2005 Chief, Gastroenterology Section, VA San Diego Healthcare System  
 2004-2009 Chief, Division of Gastroenterology, University of California, San Diego  
 2005-2009 Professor of Medicine (tenured), University of California, San Diego  
 2007-2010 Director, UCSD Gastroenterology NIH T32 Training Grant  
 2007-2009 Director, UCSD NIH Digestive Diseases Research Development Center (DDRDC)  
 2008-2009 co-Program Leader, Reducing Cancer Disparities, UCSD Comprehensive Cancer Center  
 2008-2012 co-PI, NCI U54 Comprehensive SDSU/UCSD Cancer Center Partnership  
 11/2009- John G. Searle Professor and Chairman, Dept. of Internal Medicine, University of Michigan

**Other Experience and Professional Memberships**

2000-2003 Editorial Board, *American Journal of Physiology: Gastrointestinal & Liver Physiology*  
 2002-2006 NIH CSR Gastrointestinal Cell and Molecular Biology Study Section (GCMB)  
 2006-2011 Board of Editors, *Gastroenterology*; Section Editor, *This Month in Gastroenterology*  
 2006-2008 National Commission on Digestive Diseases (appointed by Elias Zerhouni, M.D.)  
 2007-2012 AGA Council; Vice-Chair (07-09) and Chair (09-12) of Gastrointestinal Oncology Section  
 2009-2010 AGA Underrepresented Minorities Committee  
 2010-2014 University of Michigan Hospitals and Health Centers Executive Board (elected)  
 2011-2016 Senior Associate Editor, *Gastroenterology*  
 2012-2017 American Association of Physicians (AAP) Councilor (elected)  
 2014-2017 University of Michigan Medical School Executive Committee (elected)

**Honors**

Alpha Omega Alpha Honor Medical Society (1988); Commonwealth Fund Medical Research Fellow, National Medical Fellowships (1988); Henry J. Kaiser Family Foundation Award, National Medical Fellowships (1989); Franklin C. McLean Award, National Medical Fellowships (1989); UCSD Department of Medicine Graduating House Staff Teaching Award (1999); Fellow, American College of Physicians (FACP) (1999); Fellow,

Principal Investigator/Program Director (Last, First, Middle): CARETHERS, John M.

American College of Gastroenterology (FACG) (2001); UCSD Gastroenterology Fellows Excellence in Clinical Teaching Award (2004); Fellow, American Gastroenterological Association (AGAF) (2005); Western Association of Physicians (2006); UCSD School of Medicine Vice-Chancellor's Award for Mentoring Excellence (2006); American Society for Clinical Investigation (2008); American Association of Physicians (2011); Institute of Medicine, National Academy of Sciences (2012); American Clinical and Climatological Association (2014); Wayne State University School of Medicine Distinguished Alumni Award (2015)

### C. Selected peer-reviewed publications (in chronological order, from a total of >110)

1. **Carethers JM**, Hawn MT, Chauhan DP, Luce MC, Marra G, Koi M, Boland CR. Competency in mismatch repair prohibits clonal expansion of cancer cells treated with *N*-methyl-*N*-nitro-*N*-nitrosoguanidine. *J Clin Invest* 1996; **98**:199-206. PMC507417.
2. Zigman AF, Lavine JE, Jones MC, Boland CR, **Carethers JM**. Localization of Bannayan-Riley-Ruvalcaba syndrome gene to chromosome 10q23. *Gastroenterology* 1997; **113**:1433-1437. PMID: 9352843
3. **Carethers JM**, Hawn MT, Greenson JK, et al. Prognostic significance of allelic loss at chromosome 18q21 for stage II colorectal cancer. *Gastroenterology* 1998; **114**:1188-1195. PMID: 9609755
4. **Carethers JM**, Furnari FB, Zigman AF, Lavine JE, Jones MC, Graham GE, Teebi AS, Huang H-JS, Ha HT, Chauhan DP, Chang CL, Cavenee WK, Boland CR. Absence of *PTEN/MMAC1* germline mutations in sporadic Bannayan-Riley-Ruvalcaba syndrome. *Cancer Res* 1998; **58**:2724-2726. PMID: 9661881
5. **Carethers JM**, Chauhan DP, Fink D, Nebel S, Bresalier RS, Howell SB, Boland CR. Mismatch repair proficiency and *in vitro* response to 5-fluorouracil. *Gastroenterology* 1999; **117**: 123-131. PMID: 1038191
6. Yashiro M, **Carethers JM**, Laghi L, Saito K, et. al. Genetic pathways in the evolution of morphologically distinct colorectal neoplasms. *Cancer Res* 2001; **60**:2676-2683. PMID: 11289147
7. Huang SC, Lavine JE, Boland PS, Newbury RO, Kolodner R, Pham T-TT, Boland CR, **Carethers JM**. Germline characterization of early-aged onset of hereditary non-polyposis colorectal cancer. *J Pediatr* 2001; **138**:629-635. PMID: 11343035
8. Chang CL, Marra G, Chauhan DP, Ha HT, Chang DK, Ricciardiello L, **Carethers JM**, et. al. Oxidative stress inactivates the DNA mismatch repair system. *Am J Physiol Cell Physiol* 2002; **283**:C148-C154. PMID: 12055083
9. Ashkortab H, Smoot DT, **Carethers JM**, Rahmanian M, Kittles R, Vosgianian G, Doura M, Nidhiry E, Naab T, Momen B, Shakhani S, Giardiello FM. High incidence of microsatellite instability in colorectal cancer from African Americans. *Clinical Cancer Res* 2003; **9**:1112-1117. PMID: 12631615
10. **Carethers JM**, Smith EJ, Behling CA, Nguyen L, Tajima A, Doctolero RT, Cabrera BL, Goel A, Arnold CA, Miyai K, Boland CR. Use of 5-fluorouracil and survival in patients with microsatellite unstable colorectal cancer. *Gastroenterology* 2004; **126**: 394-401. PMID: 14762775
11. Jung B, Doctolero RT, Tajima A, Nguyen AK, Keku T, Sandler RS, **Carethers JM**. Loss of activin receptor type 2 protein expression in microsatellite unstable colorectal cancers. *Gastroenterology* 2004; **126**:654-659. PMID: 14988818
12. Goel A, Arnold CN, Niedzwiecki D, **Carethers JM**, Wasserman L, et al. Frequent inactivation of PTEN by promoter hypermethylation and its association with microsatellite instability-high (MSI-H) in sporadic colorectal cancers. *Cancer Res* 2004; **64**:3014-3021. PMID: 15126336
13. Tajima A, Hess M, Cabrera BL, Kolodner R, **Carethers JM**. The mismatch repair complex hMutS recognizes 5-fluorouracil-modified DNA as a mechanism for chemosensitivity. *Gastroenterology* 2004; **127**:1678-1684. PMID: 15578504
14. Satia JA, Keku T, Galanko JA, Martin C, Doctolero RT, Tajima A, Sandler RS, **Carethers JM**. Diet, lifestyle, and genomic instability in the North Carolina Colon Cancer Study. *Cancer, Epidemiol, Biomarkers, and Prevention* 2005; **14**:429-436. PMID: 15734969
15. Ashktorab H, Smoot DT, Farzanmehr H, Fidelia-Lambert M, Momen B, Hyland L, Iacoso-Dononue C, **Carethers JM**, Goel A, Boland CR, Giardiello FM. Clinicopathological features and MSI in colorectal cancers from African Americans. *International Journal of Cancer* 2005; **116**:914-919. PMID: 15856472
16. **Carethers JM**. Unwinding the heterogeneous nature of hamartomatous polyposis syndromes. *JAMA* 2005; **294**:2498-2500. PMID: 16287964
17. Jung B, Smith EJ, Doctolero RT, Gervaz P, Alonso JC, Miyai K, Keku T, Sandler RS, **Carethers JM**. Influence of target gene mutation on survival, stage, and histology in sporadic microsatellite unstable colon cancers. *International Journal of Cancer* 2006; **118**:2509-2513. PMID: 16380996

Principal Investigator/Program Director (Last, First, Middle): CARETHERS, John M.

18. Beck SE, Jung BH, Fiorino A, Gomez J, Del Rosario E, Cabrera BL, Huang SC, Chow JYC, and **Carethers JM**. Bone morphogenetic protein signaling and growth suppression in colon cancer. *Am J Physiology GI & Liver Physiology* 2006; **291**:G135-G145. PMID: 16769811
19. Jung BH, Beck SE, Cabral J, Chau E, Cabrera BL, Fiorino A, Smith EJ, Bocanegra M, **Carethers JM**. *Activin type 2 receptor* restoration in MSI-H colon cancer suppresses growth and enhances migration with activin. *Gastroenterology* 2007; **132**:633-644. PMID: 17258738.
20. Beck SE, Jung B, Del Rosario E, Gomez J, **Carethers JM**. BMP-induced growth suppression in colon cancer cells is mediated by p21/WAF1 stabilization and modulated by RAS/ERK. *Cell Signal* 2007; **19**:1465-1472. PMID: 17317101
21. Beck SE, **Carethers JM**. BMP suppresses *PTEN* expression via RAS/ERK signaling. *Cancer Biol & Ther*, **6**:1313-1317, 2007. PMID: 18059158
22. Chow JYC, Quach KT, Cabrera BL, Cabral JA, Beck SE, **Carethers JM**. RAS/ERK modulates TGF $\beta$ -regulated *PTEN* expression in human pancreatic adenocarcinoma cells. *Carcinogenesis*; **28**:2321-2327, 2007. PMID: 17638924
23. Shin SK, Nagasaka T, Jung BH, Matsubara N, Kim WH, **Carethers JM**, Boland CR, Goel A. Epigenetic and genetic alterations in Netrin-1 receptors UNC5C and DCC in human colon cancer. *Gastroenterology*; **133**:1849-1857, 2007. PMID: 18054557
24. Chow JYC, Dong H, Quach KT, Nguyen PNV, Chen K, **Carethers JM**. TGF $\beta$  mediates *PTEN* suppression and cell motility through calcium-mediated PKC $\alpha$  activation in pancreatic cancer cells. *Am J Physiol Gastrointest Liver Physiol*, **294**:G899-G905, 2008. PMID: 18239055
25. Grady WM and **Carethers JM**. Genomic and epigenetic instability in colorectal cancer pathogenesis. *Gastroenterology* **135**:1079-1099, 2008. PMC2866182.
26. Chow JYC, Cabral JA, Chang J, **Carethers JM**. TGF $\beta$  modulates *PTEN* expression independently of SMAD signaling for growth proliferation in colon cancer cells. *Cancer Biol & Ther* **7**:1694-1699, 2008. PMC2820113
27. Chung H, Young DJ, Lopez C, Le T-AT, Lee JK, Ream-Robinson D, Huang SC, **Carethers JM**. Mutation rates of *TGFB2* and *ACVR2* coding microsatellites in human cells with defective DNA mismatch repair. *PLoS ONE* **3**:e3463, 2008. PMC2565065.
28. Jung BH, Gomez J, Chau E, Cabral J, Lee JK, Anselm A, Slowik P, Ream-Robinson D, Messer K, Sporn J, Shin SK, Boland CR, Goel A, **Carethers JM**. Activin signaling in microsatellite stable (MSS) colon cancers is disrupted by a combination of genetic and epigenetic mechanisms. *PLoS ONE*, **4**:e8308, 2009. PMC2789408.
29. Chow JYC, Ban M, Wu HL, Nguyen F, Huang M, Chung H, Dong H, **Carethers JM**. TGF $\beta$  downregulates *PTEN* via activation of NF- $\kappa$ B in Pancreatic Cancer Cells. *Am J Physiol Gastrointest Liver Physiol*, **298**:G275-82, 2010. PMID: 19940030
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31. Chung H, Lopez CG, Holmstrom J, Young DJ, Lai JF, Ream-Robinson D, **Carethers JM**. Both microsatellite length and sequence context determine frameshift mutation rates in defective DNA mismatch repair. *Hum Mol Genet* **19**:2638-47, 2010. PMC2912546.
32. Ghosh P, Beas AO, Bornheimer SJ, Garcia-Marcos M, Forry EP, Johansson C, Ear J, Jung BH, Cabrera B, **Carethers JM**, Farquhar MG. A Gi-G1V molecular complex binds epidermal growth factor receptor and determines whether cells migrate or proliferate. *Mol Biol Cell* **21**:2338-54, 2010. PMC2893996.
33. Deveraj B, Lee A, Cabrera BL, Miyai K, Luo L, Ramamoorthy S, Keku T, Sandler RS, McGuire K, **Carethers JM**. Relationship of EMAST and microsatellite instability among patients with rectal cancer. *J Gastrointest Surg* **14**:1521-8, 2010. PMC2943582.
34. Lee S-Y, Chung H, Deveraj B, Iwaizumi M, Han HS, Hwang D-Y, Seong MK, Jung BH, **Carethers JM**. Elevated microsatellite alterations at selected tetranucleotide repeats are associated with morphologies of colorectal neoplasia. *Gastroenterology* **139**:1519-1525, 2010. PMC2967646.
35. Chung H, Chaudhry J, Lopez, CG, **Carethers JM**. Cyclin E and histone H3 are regulated by 5-fluorouracil in a DNA mismatch repair-dependent manner. *Cancer Biol & Ther* **10**:1147-1156, 2010. PMC3230292.

Principal Investigator/Program Director (Last, First, Middle): CARETHERS, John M.

36. Dong H, Shim K-N, Li J, Estrema C, Orneles T, Nguyen F, Liu S, Ramamoorthy S, Ho S, **Carethers JM**, Chow JYC. Molecular mechanisms underlying  $\text{Ca}^{2+}$ -mediated motility of human pancreatic duct cells. 2010. *Am J Physiol Cell Physiol* **299**:C1493-1503, 2010. PMC3006328.
37. Huang SC, Lee JK, Smith EJ, Doctolero R, Tajima A, Beck SE, Weidner N, **Carethers JM**. Evidence for an hMSH3 defect in familial hamartomatous polyps. *Cancer* **117**:492-500, 2011. PMC3005073
38. Garcia-Marcos M, Jung BH, Ear J, Cabrera BL, **Carethers JM**, Ghosh P. The expression of GIV/Girdin, a metastasis-related protein, predicts patient survival in colon cancer. *FASEB J* **25**:590-599, 2011. PMC3023389
39. Iwaizumi M, Tseng-Rogenski S, **Carethers JM**. DNA mismatch repair proficiency executing 5-fluorouracil cytotoxicity in colorectal cancer cells. *Cancer Biol Ther* **12**:756-764, 2011. PMC3367669
40. Tajima A, Iwaizumi M, Tseng-Rogenski S, Cabrera BL, **Carethers JM**. Both hMutS $\alpha$  and hMutS $\beta$  complexes participate in 5-fluorouracil cytotoxicity. *PLoS ONE*, **6**:e28117, 2011. PMC3229514
41. Lee S-Y, Miyai K, Han HS, Hwang D-Y, Seong MK, Chung H, Jung BH, Devaraj B, McgGuire KL, **Carethers JM**. Microsatellite instability, EMAST, and morphology associations with T cell infiltration in colorectal neoplasia. *Dig Dis Sci*, **57**:72-8, 2012. PMC3245369
42. Chung H, Chaudhry J, Lai JF, Young DJ, **Carethers JM**. Flanking nucleotide specificity for DNA mismatch repair-deficient frameshifts within *Activin Receptor 2 (ACVR2)*. *Mutat Res*, **729**:73-80, 2012. PMC3237829
43. Ayanian JZ and **Carethers JM**. Bridging Behavior and Biology to Reduce Socioeconomic Disparities in Colorectal Cancer Risk. *J Natl Cancer Inst* **104**:1343-1344, 2012. PMCID: pending
44. Tseng-Rogenski S, Chung H, Wilk MB, Zhang S, Iwaizumi M, **Carethers JM**. Oxidative stress induces nuclear-to-cytosol shift of hMSH3, a potential mechanism for EMAST in colorectal cancer cells. *PLoS ONE* **7**:e50616, 2012. PMC3511561
45. Iwaizumi M, Tseng-Rogenski S, **Carethers JM**. Acidic tumor microenvironment downregulates hMLH1 but does not diminish 5-fluorouracil chemosensitivity. *Mutat Res* **747-748**:19-27, 2013. PMC3770844
46. Ashktorab J, Wansley D, Rahi J, Varma S, Shokrani B, Lee E, Daremipouran M, Laiyemo A, Goel A, **Carethers JM**, Brim H. Toward a comprehensive and systemic methylome signature in colorectal cancers. *Epigenetics* **8**:807-815, 2013. PMCID: PMC3883784
47. **Carethers JM**. DNA testing and molecular screening for colon cancer. *Clin Gastroenterol Hepatol* **12**:377-381, 2014. PMCID: PMC4151968
48. **Carethers JM**. Differentiating Lynch-like from Lynch syndrome. *Gastroenterology* **146**:602-604, 2014. PMCID: PMC4134259
49. **Carethers JM**, Murali B, Yang B, Doctolero RT, Tajima A, Basa R, Smith EJ, Lee M, Janke R, Ngo T, Tejeda R, Ji M, Kinseth M, Cabrera BL, Miyai K, Keku TO, Martin CF, Galanko JA, Sandler RS, McGuire KL. Influence of race on microsatellite instability and CD8<sup>+</sup> T cell infiltration in colon cancer. *PLoS ONE* **9**:e100461, 2014. PMCID: PMC4067325
50. **Carethers JM**. Screening for colorectal cancer in African Americans: Determinants and rationale for an earlier age to commence screening. *Dig Dis Sci* 2015. (in press) PMCID: pending
51. Tseng-Rogenski S, Hamaya Y, Choi D, **Carethers JM**. Interleukin 6 alters localization of hMSH3, leading to DNA mismatch repair defects in colorectal cancer cells. *Gastroenterology* 2015. (in press) PMCID: pending

#### D. Research Support ongoing or completed during the last three years

##### R01 DK067287 Carethers (PI)

09/1/05 to 08/31/16

NIH/NIDDK

Microsatellite Instability and the DNA Mismatch Repair System

**Major goals:** To determine the role and expression of the DNA mismatch repair protein hMSH3 in preventing mutation of human DNA at microsatellite sequences.

##### U01 CA162147 Carethers (PI)

09/01/12 to 08/31/17

Inflammatory Differentiation of Colorectal Cancer among African Americans

**Major goals:** To evaluate the role of mismatch repair dysfunction and immune and cytokine profiles within colorectal cancers from diverse populations.

Principal Investigator/Program Director (Last, First, Middle): Baines, Antonio, T.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Baines, Antonio Thomas</b>	POSITION TITLE Associate Professor of Biology and the Cancer Research Program		
eRA COMMONS USER NAME			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Norfolk State University	B.S.	1995	Biology
University of Arizona	Ph.D.	2001	Pharmacology/ Toxicology
University of North Carolina at Chapel Hill	Postdoc	2006	Pharmacology

**A. Personal Statement**

I have been interested in molecular targeted therapy of pancreatic cancer for almost 8 years since completion of my postdoc studying oncogenic Ras signaling in pancreatic cancer under Dr. Channing Der. The overall focus of our cancer biology research program is to discover novel molecular targets in cancer, especially pancreatic cancer, which can be targeted by potential cancer therapeutics. We want to understand the role of these molecular targets in the development and progression of normal cells transforming into cancer cells of the pancreas. Most recently, we have become interested in molecular targets that are involved in drug resistance of pancreatic cancer to gemcitabine. Also, we have an interest in the health disparity seen with pancreatic cancer. We look forward to investigating the underlying role biology may contribute to the increased incidence and worse prognosis observed in certain populations.

**B. Positions and Honors****Positions and Employment**

2006-	Assistant Professor of Biology & the Cancer Research Program, J. L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, North Carolina
2008-	Adjunct Assistant Professor of Pharmacology, School of Medicine, UNC-Chapel Hill, Chapel Hill, North Carolina
2011-2012	Consultant, Jasco Pharmaceuticals
2013-	Associate Professor of Biology & the Cancer Research Program, J. L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, North Carolina
2013-	Adjunct Associate Professor of Pharmacology, School of Medicine, UNC-Chapel Hill, Chapel Hill, North Carolina

Principal Investigator/Program Director (Last, First, Middle): Baines, Antonio, T.

- 2014- Member, Curriculum in Toxicology, Graduate School, UNC-Chapel Hill, Chapel Hill, North Carolina
- 2014 Consultant, Clarion Healthcare, LLC

**Professional Memberships and Selected Experiences**

- 1997- Society of Toxicology
- 1997- American Association for Cancer Research
- 2011 *Ad Hoc* Reviewer, NIH Molecular and Integrative Signal Transduction (MIST) Study Section
- 2011 Reviewer, European Journal of Cancer
- 2012- HHMI Grant EXROP Study Section
- 2015 *Ad Hoc* Reviewer, NIH Cancer Drug Development and Therapeutics (CDDT) Study Section

**Selected Honors and Presentations**

- 2006 Invited Seminar Speaker, Gastroenterology Division Research Conference, Duke University Medical Center, Durham, NC
- 2007 Invited Seminar Speaker, Department of Pharmacology Seminar Series, UNC-Chapel Hill, Chapel Hill, NC
- 2011 Society of Toxicology-Toxicologists of African Origin (TAO) Mentor/Educator Award
- 2012 American Association for Cancer Research Minority-Serving Institution Faculty Scholar Awardee
- 2012 Invited Seminar Speakers – Department of Pharmacology and Toxicology– School of Medicine, Indiana University, Indianapolis, IN; Department of Environmental and Molecular Toxicology – NC State University, Raleigh, NC
- 2013 Invited Seminar Speaker – Pharmacology and Toxicology Division – University of Missouri-Kansas City, Kansas City, MO
- 2013 Invited Seminar Speaker – Department of Biology – Massachusetts Institute of Technology (MIT), Boston, MA
- 2014 Invited Seminar Speaker - Eppley Cancer Institute, University of Nebraska Medical Center, Omaha, NE
- 2014 Invited Seminar Speaker – Tolero Pharmaceuticals, Lehigh, UT

**C. Selected Publications**

1. Sauer JM, Hooser SB, Badger DA, **Baines AT**, Sipes IG. (1995) Alterations in chemically induced tissue injury related to all-trans retinol pretreatment in rodents. *Drug Metabolism Reviews* 27(1&2):299-323.
2. Sauer JM, Waalkes MP, Hooser SB, **Baines AT**, Kuester RK, Sipes IG. (1997) Tolerance induced by all-trans-retinol to the hepatotoxic effects of cadmium in rats: role of metallothionein expression. *Toxicology and Applied Pharmacology* 143:110-119.
3. **Baines AT**, Holubec H, Basye JL, Thorne P, Bhattacharyya AK, Spallholz J, Shriver B, Cui H, Roe D, Clark LC, Earnest DL, Nelson MA. (2000) The effects of dietary selenomethionine on polyamines and azoxymethane-induced aberrant crypts. *Cancer Letters* 160:193-198.
4. Lim, K.-H., **Baines, A.T.**, Fiordalisi, J.J., Shipitsin, M., Feig, L.A., Cox, A.D., Der, C.J., and Counter, C.M.: (2005) Activation of RalA is critical for Ras-induced tumorigenesis of human cells. *Cancer Cell* 7:533-545. [PMC15950903]

Principal Investigator/Program Director (Last, First, Middle): Baines, Antonio, T.

5. **Baines, A.T.**, Lim, K.-H., Shields, J.M., Lambert, J.M., Counter, C.M., Der, C.J., and Cox, A.D.: Use of retrovirus expression of interfering RNA to determine the contribution of activated K-Ras and Ras effector expression in human tumor cell growth. Methods in Enzymology. Vol. 407, pp. 556-74, 2005.
6. Xu, D., Allsop, S.A., Witherspoon, S.M., Snider, J.L., Yeh, J.J., Fiordalisi, J.J., White, C.D., Williams, D., and **Baines, A.T.**: (2011) The oncogenic kinase Pim-1 is modulated by K-Ras signaling and mediates transformed growth and radioresistance in human pancreatic ductal adenocarcinoma cells. *Carcinogenesis*, 32(4):488-95. [PMC3066419]
7. **Baines, A.T.**, Xu, D., and Der, C.J.: Inhibition of Ras for cancer treatment: the search continues. Future Medicinal Chemistry, 1787-1808, 2011.
8. Xu, D., Cobb, M., Gavilano, L., Sam Witherspoon, S.M., Williams, D., White, C.D., Taverna, P., Bednarski, B., Hong Kim, H.J., Baldwin, A., and **Baines, A.T.**: (2013) Inhibition of oncogenic Pim-3 kinase modulates transformed growth and chemosensitizes pancreatic cancer cells to gemcitabine. *Cancer Biology & Therapy*, 14:6, 1-10. [PMC3813565]

#### D. Selected Research Support

NCCU/UNC-Lineberger U54 Partnership in Cancer Research Grant-NCI 08/2013-08/2015  
 "Identification of the Pim kinome in pancreatic cancer"  
 Role: Co-Investigator

Jasco Pharmaceuticals Collaborative Grant, "Pim kinase inhibitors in pancreatic cancer"  
 01/11-07/12  
 Role: PI

Duke-NCCU STEM Partnership Grant, "The role of Pim-1 kinase as a novel molecular target in pancreatic cancer" 09/01/08-11/30/09  
 Role: Co-Investigator

NCI/NIGMS MBRS Support of Competitive Research (SCORE) Pilot Project Award (SC2), entitled "The role of Pim kinases as a novel molecular target in pancreatic cancer" 08/01/08-07/31/12  
 Role: PI

Academy of Applied Science and the Army Research Office; Support high school students conducting research during the summers 2008-  
 Role: Co-Investigator

NCCU-BBRI/UNC-Lineberger Partnership in Cancer Research Pilot Grant, "Molecular targets in pancreatic cancer" 10/14/06-04/30/08  
 Role: Co-Investigator

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Fraser- White, Marilyn	POSITION TITLE Deputy Director		
eRA COMMONS USER NAME (credential, e.g., agency login) Mwhite30			
EDUCATION/TRAINING ( <i>Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.</i> )			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
City University of New York at Brooklyn College	BA	02/94	Chemistry
Spartan Health Sciences University School of Medicine	MD	04/00	Medicine

### A. Personal Statement

My experience in conducting community based research, as part of a community-based organization (Arthur Ashe Institute for Urban Health) with long-standing relationships within the community, as well as my leadership roles in the Brooklyn Health Disparities Center will be important to my role in an advisory capacity. In addition to my role as the Deputy Executive Director for the Arthur Ashe Institute, I serve as the Director of the Community Engagement Core of the NIH-NIMHD funded Brooklyn Health Disparities Center, a partnership between the SUNY Downstate Medical Center, the Arthur Ashe Institute for Urban Health, and the Office of the Brooklyn Borough President. In this capacity, my responsibilities include coordinating and supervising the development and implementation of a health disparities curriculum for high school students as well as a curriculum for community leaders to increase their capacity to conduct research. As part of a team of researchers working on a CDC funded project to develop a barbershop based HIV/AIDS risk reduction intervention for African American men, I have supervised the recruitment and formative phase of the project, and have collaborated with other investigators to develop the training modules for the intervention. I have also served as the principal investigator for a grant, funded by the New York University – Clinical & Translational Science Institute, to develop and pilot a cardiovascular disease (CVD) risk reduction intervention to train salon stylists to deliver heart health messages, including stress reduction messages, to their customers. I have coordinated many of the Institute's outreach programs, including the federally funded programs, and was instrumental in developing the Institute's salon and barbershop based programs into behavioral health intervention models. I have also served as a co-investigator for the Institute's ACCESS program to increase access to health and social resources for formerly incarcerated individuals and their families. As an NIH LRP award recipient, I conducted preliminary work to assess CVD risk factors among formerly incarcerated Black men. Additionally, I served as part of an investigative team of researchers to develop training curricula on various topics including cardiovascular disease, cancer (breast, prostate and colorectal), diabetes, HIV/AIDS, health disparities and community based participatory research. Most recently, I was the recipient of the Fulbright Research Specialist award. Given my vast experience in developing and conducting community health disparities intervention programs and leading the community engagement efforts of the Institute and the Brooklyn Health Disparities Center, I am well prepared to serve as a member of the advisory board.

### B. Positions and Honors.

#### Positions and Employment

1994-1996	<i>Public Health Advisor</i> , New York City Department of Health, Bureau of Tuberculosis Control (Regulatory Affairs), New York, NY,
2000-2001	<i>Outreach Coordinator/ Program Director (Acting)</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2001-2004	<i>Research Manager</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2003-present	<i>Instructor</i> , Health Science Academy (Arthur Ashe Institute)
2004-2012	<i>Associate Director, Research &amp; Training</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2007	<i>Acting Deputy Director</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY
2012-present	<i>Deputy Director</i> , Arthur Ashe Institute for Urban Health, Brooklyn, NY

### **Awards/ Honors**

Steven Biko Memorial Scholarship (1988)  
Minority Access to Research Careers (MARC) Fellowship (1988-1990)  
Sigma-Xi Rudin Fellowship Award (1990)  
SIPID Scholar (2008)  
Project Interchange Alumni (2008)  
Health Award (New York State Association of Black & Puerto Rican Legislators, Inc.) (2011)  
Extraordinary Women of Downstate Award (2012)  
NIH Loan Repayment Program award recipient (2012-2014)  
New York State Department of Health – Commissioner’s Special Recognition Award (2013)  
Fulbright Research Specialist Fellowship Award (2013)  
Innovator Award – Bedford Stuyvesant Family Health Center (2014)

### **C. Contribution of Science**

#### **1. Development of Culturally Tailored Interventions**

I have worked closely with members of the community and faculty at various institutions to develop and implement culturally tailored curricula on various health issues such as prostate cancer, HIV/AIDS and cardiovascular disease.

- a. Brown N, Naiman P, Homel P, Fraser-White M, Clare R, Browne R. (2006). Assessment of preventive health knowledge and behaviors of African-American and Afro-Caribbean women in urban settings. *J Natl Med Assoc.*, 98(10), 1644-1651. PMID: PMC2569737
- b. Fraser M, Brown H, Homel P, Macchia RJ, LaRosa J, Clare R, Davis-King D, Collins P, Samuel T, Macalino G, Browne R. (2009) Barbers as Lay Health Advocates – Developing a Prostate Cancer Curriculum. *J Natl Med Assoc.*, 101(7), 690-697. PMID: 19634590
- c. Brown, N., Vaughn, N.A., Lin, A.J., Browne, R., White, M., & Smith, P. (2011) Healthy Families Brooklyn: Working with Health Advocates to Develop a Health Promotion Program for Residents Living in New York City Housing Authority Developments. *J. Community Health*, 36(5), 864-873. PMID: 21400120
- d. Boutin-Foster C, George K, Samuel T, Fraser-White M, Brown H. (2008). Training Community Health Workers to be Advocates for Health Promotion: Efforts Taken by a Community-Based Organization to Reduce Health Disparities in Cardiovascular Disease. *Journal of Community Health*, 33(2), 61-68. PMID:18058210

#### **2. Replication of Innovative Science Models**

As part of an investigative team of researchers, I have worked on the replication of the Institute’s community outreach efforts in non-traditional settings. As a recipient of a Fulbright Research Specialist award, I developed and implemented a program on climate change and public health in collaboration with the University of the West Indies. I am currently working as a co-investigator on a pilot project across universities in the West Indies and various State Universities of New York to assess cardiovascular disease risk in individuals of Caribbean descent in New York and those in their native Caribbean countries.

- a. Browne R, Vaughn NA, Siddiqui N, Brown N, Delmoor E, Randleman P, Randleman S, Gonzalez L, Lewis J, Lourie R, Foster G, Brown H, Fraser-White M, Banks S. (2009) Community-Academic Partnerships: Lessons Learned from Replicating a Salon-Based Health Education and Promotion Program. *Progress in Community Health Partnerships: Research, Education and Action*, 3(3), 241-248. PMID: 2020822
- b. Henry KR, Fraser-White M, Roberts CR, Wilson TE, Morgan R, Brown H, Shaw R, Jean-Louis G, Graham YJ, Brown C, Browne R. (2012) Engaging Minority High School Students as Health Disparities Interns: Findings and Policy Implications of a Summer Youth Pipeline Program. *J Natl Med Assoc.*, 104 (9, 10), 412-419

#### **3. Community Engaged Research**

One of my contributions to science has been my extensive work in the community, in developing, implementing and assessing interventions that are focused on addressing health disparities and reducing risk factors for disease.

- a. Clark, L, Browne, R., Kokolis, R., White, M., Morales, S.: Health Disparities and Cardiovascular Disease, in Clark, LT (ed.): Cardiovascular Disease and Diabetes: Modern Management. New York, McGraw-Hill, 2006; p 506
- b. Wilson T, Fraser-White M, Feldman J, Homel P, Wright S, King G, Coll B, Banks S, Davis-King D, Price M, Browne R. (2008). Hair salon stylists as breast cancer prevention lay health advisors for African American and Afro-Caribbean women. Journal of Health Care for the Poor and Underserved, 19, 216-226. PMID:18263997
- c. Wilson TE, Fraser-White M, Williams KM, Pinto A, Agbetor F, Camilien B, Henny K, Browne RC, Gousse Y, Taylor TN, Brown H, Taylor RD, Joseph MA. Barbershop Talk with Brothers: Using Community-Based Participatory Research to Develop and Pilot Test a Program to Reduce HIV Risk among Black Heterosexual Men. AIDS Educ Prev 2014 Oct;26(5):383-97
- d. Taylor TN, Joseph MA, Henny KD, Pinto AR, Agbetor F, Camilien B, Williams KM, Browne RC, White M, Gousse Y, Brown H, Taylor RD, Wilson TE. Perceptions of HIV risk and explanations of sexual risk behavior offered by heterosexual Black male barbershop patrons in Brooklyn, NY. Journal of Health Disparities Research and Practice [forthcoming].

#### 4. Community Based Participatory Research (CBPR)

The importance of fostering community-academic partnerships is essential to the success of research efforts that are focused on eliminating health disparities. I have had the opportunity to develop and implement training activities for community based organizations and faculty on CBPR. I have worked closely with CBO's on increasing the capacity of community numbers to conduct research

- a. Roberts CB, Browne R, Wilson TE, Morgan R, Brown H, Shaw R, Jean-Louis G, Brown C, Fraser-White M. Lessons Learned from Building an Infrastructure for Community-Based Participatory Research. International Public Health Journal [in press]
- b. Henry KR, Fraser-White M, Roberts CR, Wilson TE, Morgan R, Brown H, Shaw R, Jean-Louis G, Graham YJ, Brown C, Browne R. (2012) Engaging Minority High School Students as Health Disparities Interns: Findings and Policy Implications of a Summer Youth Pipeline Program. J Natl Med Assoc., 104 (9, 10), 412-419

### 5. Research Support

#### Ongoing Research Support

HHSN276201400887P

National Library of Medicine Fraser-White (PI)

09/30/14 – 09/29/15

"AAIUH mHealth HIV/AIDS Risk Reduction Initiative"

The goal of the project is to facilitate and improve access to NLM's HIV/AIDS medical information and educational resources for high-need individuals, caregivers, family, friends and other community members.

Role: Director

P1-12-001

Jensen, Levine (PIs)

07/01/12 – 06/30/14

PCORI

"Mobile Apps (MAPPS): Patient & Caregiver Attitudes, Behaviors & Knowledge"

The aim of this collaborative project is to explore the needs, attitudes, knowledge, and behavior toward M-tech for health management within the model of stroke, as stroke survivors and their caregivers require continuous monitoring and informational updates.

Role: Co-investigator

1P20MD006875-01

Browne, Salifu (PIs)

06/14/12 – 01/31/17

NIH - NIMHD

"Brooklyn Health Disparities Center – Community Engagement"

The goal of this grant is to strengthen the capacity of the Brooklyn Health Disparities Center through its community engagement core by developing and implementing a health disparities curriculum for high school students and a curriculum on community based participatory research to increase the capacity of local community based organizations.

Role: Director – Community Engagement

NIH-Loan Repayment Program (LRP) Fraser-White (PI) 2012-2014

“ACCESS Project for Formerly Incarcerated Individuals”

The goal of this grant is to assess cardiovascular disease risk factors among formerly incarcerated individuals.

Role: Loan Repayment Program Participant

### **Completed Research Support**

New York Department of Health

03/15/12-07/15/12

*Communities of Color Condom Distribution Project*

The goal of this project is to raise awareness about HIV/AIDS among minorities, through distribution of condoms and information on HIV/AIDS (i.e. brochures, pamphlets and video documentary), in non-traditional venues such as barbershops and salons in Central Brooklyn.

Role: Director

1UL1RR029893

White (PI)

03/29/10-03/28/11

NYU-HHC CTSI

*“Heart of a Woman”*

The goal of this grant is to pilot a cardiovascular disease curriculum to train community- based professional stylists, as messengers, to deliver heart health messages to their customers to promote healthy behaviors that will reduce risk of cardiovascular disease in minority women.

Role: Principal Investigator

1P20MD005092-01

Brown, Browne, Wilson (PIs)

09/30/09 – 07/31/12

NIH - NCMHD

*“Brooklyn Health Disparities Center – Community Engagement”*

The goal of this grant is to strengthen the capacity of the Brooklyn Health Disparities Center through its community engagement core by developing and implementing a health disparities curriculum for high school students and a curriculum on community based participatory research to increase the capacity of local community based organizations.

Role: Director – Community Engagement

1 UR6 PS000691-01,  
CDC

Wilson (PI)

09/01/07 – 02/29/12

*“Reducing HIV Heterosexual Risk among African-American Men”*

The overall goal of this project is to develop a program that will reach heterosexual men in barbershops serving communities with high HIV morbidity and AIDS related mortality;

Role: Co-Investigator

Empire BlueCross BlueShield

Browne (PI)

01/01/11-12/31/11

*“Heart of a Woman”*

The goal of this grant is to implement a cardiovascular disease intervention program in which professional salon stylists are trained to deliver heart health messages to their customers to promote healthy behaviors that will reduce risk of cardiovascular disease in minority women.

Role: Co-Investigator

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Samuel Ryu M.D.</b>		POSITION TITLE <b>Professor &amp; Chair, Dept of Radiation Oncology</b>	
eRA COMMONS USER NAME (credential, e.g., agency login) <b>Saryu1</b>			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Kyungpook University School of Medicine, Korea	M.D.	1982	Medicine
Kyungpook University Graduate School, Korea	M.S.	1988	Radiology
Yonsei and Kyungpook University Hospital, Korea	Residency	1986-1989	Radiation Oncology
Henry Ford Hospital, Detroit, MI	Post-doc	1991-1993	Tumor and Radiation Biology
Henry Ford Hospital, Detroit, MI	Residency	1993-1996	Radiation Oncology

**A. Personal Statement:**

As Chair of the Department of Radiation Oncology, I have a strong commitment to the diagnosis, treatment and research of GI cancers. In fact our department is launching a new clinical protocol for treating unresectable/borderline resectable pancreatic adenocarcinoma with SBRT/chemotherapy. My department is consequently very interested in the development of pancreatic organoids from EUS-FNB biopsies, which may serve as a model for assessing the most effective therapy for individual cases of pancreatic cancer.

**B. Positions and Honors:**

1989-1993	Assistant Professor, Radiation Oncology, Kyungpook University Hospital, Korea
1996-1999	Assistant Professor of Radiation Oncology, Upstate Medical Center, Syracuse, NY
1999-2014	Senior Staff, Radiation Oncology, Henry Ford Hospital, Detroit, Michigan
2000-2014	Director, Center for Radiosurgery, Henry Ford Hospital
2005-2014	Leader, Neuro and Spine Oncology/ Spine Tumor Board, Henry Ford Health System
2010-2011	NCI Study Section, Clinical Studies Special Emphasis Panel
2010-	Founding Editor-in-chief, Journal of Radiosurgery and SBRT
2013-2015	President, International Stereotactic Radiosurgery Society
2014-	Professor and Chair, Radiation Oncology, Stony Brook University School of Medicine
2014-	Deputy Director for Clinical Affairs, Stony Brook Cancer Center

**C. Peer-reviewed Publications: (selected)**

1. Kleinberg L, Supko JG, Mikkelsen T, Blakeley JO, Stevens G, Ye X, Desideri S, **Ryu S**, Desai B, Giranda VL, Grossman SA. Phase I adult brain tumor consortium (ABTC) trial of ABT-888 (veliparib), temozolomide (TMZ), and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM) including pharmacokinetic (PK) data. *Journal of Clinical Oncology*. 2013;31(15).
2. Kim EY, Yechieli RL, Kim JK, Mikkelsen T, Kalkanis S, Rock JP, **Ryu S**. Patterns of Failure after Radiosurgery to different target volumes of enhancing lesion only versus enhancing lesion and FLAIR abnormality for recurrent Glioblastoma Multiforme. *Journal of Neuro-oncology* 116:291-297. 2014 doi: 10.1007/s11060-013-1290-1294. Epub 2013 Oct 31. PMID: 24173682
3. **Ryu S**, Ryken T, Olson J, Kalkanis S. The role of radiotherapy in the management of progressive glioblastoma multiforme. *Journal of Neuro-oncology* 18(3):489-99, 2014. doi: 10.1007/s11060-013-1337-6. Epub 2014 Apr 12.
4. Zhao B, Jin JY, Wen N, Huang Y, Siddiqui MS, Chetty I, **Ryu S**. Prescription to 50-75% isodose line may be

Program Director/Principal Investigator (Last, First, Middle):

- optimum for linear accelerator based radiosurgery of cranial lesions. *Journal of Radiosurgery and SBRT* 2014
5. Jin JY, Huang Y, Brown SL, Movsas M, Chetty IJ, **Ryu S**, Kong FM. Radiation dose-fractionation effects in spinal cord: comparison of animal and human data. *Physics in Medicine and Biology* 2014 (in print)
  6. Huang Y, Chin K, Robbins J, Kim J, Li, H, Amro H, Chetty IJ, Gordon J, **Ryu S**. Radiosurgery of multiple brain metastases with single-isocenter dynamic conformal arcs (SIDCA). *Radiotherapy and Oncology* 112(1):128-32, 2014. doi: 10.1016/j.radonc.2014.05.009. Epub 2014 Jul 2
  7. Chin K, Ryu S. The Use of Jaw Tracking in Intensity Modulated and Volumetric Modulated Arc Radiotherapy for Spine Stereotactic Radiosurgery. *Practical Radiation Oncology* 2014 PRACTICALRADONC-D-14-00138R1
  8. Bellon M, Siddiqui MS, Ryu S, Chetty I. The effect of longitudinal CT resolution and pixel size (FOV) on target delineation and treatment planning in stereotactic radiosurgery. *Journal of Radiosurgery and SBRT* 2014
  9. Robbins JR, Kim SR, Kalkanis S, Cogan C, Rock J, Rosenblum M, Kim JH, **Ryu S**. Stereotactic radiosurgery in the multidisciplinary management of large (target volume  $\geq 20$  cc or  $\geq 3$  cm in diameter) brain metastases. *Journal of Neurosurgery* 2014
  10. Fisher BJ, Hu C, Macdonald DR, Lesser GJ, Coons S, Brachman DG, **Ryu S**, Werner-Wasik M, Bahary JP, Liu J, Chakravati A, Mehta MP. Phase II study of a Temozolomide-based chemoradiotherapy regimen for high-risk low-grade gliomas: Results of RTOG 0424. *International Journal of Radiation Oncology Biology Physics* 91(3): 497-504, 2015
  11. Lo SS, Ryu S, Chang EL, Galanopoulos N, Jones J, Kim EY, Kubicky CD, Lee CP, Rose PS, Sahgal A, Sloan AE, The BS, Traughber BJ, Poznak CV, Vassil, AD. American College of Radiology ACR Appropriateness Criteria® Expert Panel on Radiation Oncology–Bone Metastases: Metastatic epidural spinal cord compression and recurrent spinal metastasis. *Journal of Palliative Medicine* 2015 (in Print)
  12. Thibault I, Lo SS, Chang EL, Sheehan J, Ahluwalia MS, Guckenberger M, Sohn MJ, Ryu S, Foote M, Muacevic A, Soltys SG, Chao S, Gerszten P, Lis E, Yu E, Bilsky M, Fisher C, Schiff D, Fehlings MG, Ma L, Chang S, Chow E, Parelukar W, Vogelbaum M. Challenges Determining Response after Stereotactic Body Radiotherapy for Spinal Metastases and Review of Current Practices: Part 1 of a First Report from the Spine Response Assessment in Neuro-Oncology (SPANO) Group. *Lancet Oncology* 2015 (under review)
  13. Redmond KJ, Robertson S, Lo SS, Soltys S, **Ryu S**, McNutt T, Chao S, Barani I, Yamada J, Ghia A, Chang EL, Sheehan J, Sahgal A. Consensus Contouring Guidelines for Post-Operative Spine Stereotactic Body Radiation Therapy. *ISRS* 2015
  14. **Ryu S**, Yoon H, Stessin A, Rosiello A, Gutman F, Davis R. Contemporary Treatment with Radiosurgery for Spine Metastasis and Spinal Cord Compression in 2015. *Radiation Oncology Journal* 2015 (in print)

## D Research Support

### ACTIVE

2009- RTOG-0631 Phase II/III study of spine radiosurgery for localized spine metastasis. (Role: National P.I. and Study chair) -- U10 CA 21661-325 (RTOG), U10 CA37422-21 (CCOP)

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Minsig Choi MD</b>	POSITION TITLE <b>Associate Professor of Medicine</b>		
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of the Philippines, Metro Manila, Philippines	BS	4/1994	Molecular Biology
Far Eastern University Manila, Philippines	MD	4/1998	Medicine
Chicago Medical School, Chicago, IL	residency	6/2003	Internal Medicine
Wayne State University, Detroit, MI	fellowship	6/2006	Hematology-Oncology

**A. Personal Statement**

I have been actively engaged in clinical and translational research in the field of gastrointestinal cancer with focus in geriatric population and their comorbidities. My research also involves close collaborations with basic researchers other medical disciplines including psychological issues. The major philosophy of my work is that the translational empiric approach in developing new treatments in this disease must be changed to a biology-driven approach. My interests include targeting signaling pathways, immunotherapy and supportive care that involves multidisciplinary approach to cancer care.

**PROFESSIONAL EXPERIENCE**

8/2014 to present Associate Professor in Department of Medicine, Stony Brook University  
Director of Outpatient Oncology

9/2010- 8/2014 Assistant Professor, in Oncology, Karmanos Cancer Institute, NCI-designated Comprehensive Cancer Center and Wayne State University, Detroit, MI

7/2006 to 9/2010, Staff Physician; G. V. Montgomery VA Medical Center Jackson, MS  
Assistant Professor, University of Mississippi, Department of Medicine, Division of Oncology

**MEMBERSHIP**

2010 to 2014 Member/ vice chair of the Phase I Institutional Review Board at Wayne State University  
2006 to 2014 Member of Southwest Oncology Group(SWOG), GI subcommittee  
2003 to present Member of American Society of Clinical Oncology (ASCO)  
2007 to 2010 Member of the Jackson VAMC Institutional Review Board  
2003-2006 served Quality Assurance Committee at Karmanos Cancer Institute/Wayne State University

Board Certification:

Program Director/Principal Investigator (Last, First, Middle):

2007- Board certified in Hematology, American Board of Internal Medicine  
 2006- Board certified in Medical Oncology, American Board of Internal Medicine  
 2003- 2013 Board certified in Internal Medicine, American Board of Internal Medicine

## HONORS/Awards

2012 WSU School of Medicine – College Teaching Award  
 2009 Travel grant from International Society of GI oncology  
 2007 Mississippi Research, “Young Investigator Award”  
 2006 Merit Award form American Society of Clinical Oncology  
 2005 Fellowship travel grant for ASCO  
 1998 cum laude for Doctor of Medicine  
 1998 Most Outstanding Medical Student Award  
 1994 cum laude for BS Molecular Biology  
 1994 Phi Kappa Phi Honor Society

## C. Selected Peer-reviewed Publications

1. Fujiki M, Aucejo F, **Choi M**, Kim R., Neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: where do we stand? *World J Gastroenterol*. 2014 May 14;20(18):5308-19.
2. **Choi M**, Kim R, Saif MW. Is there a role for 2<sup>nd</sup> line chemotherapy in pancreatic cancer? *Journal of Pancreas* 2014 Mar 10;15(2):106-9
3. Yano H, Thakur A., **Choi M**, et. al. Ipilimumab augments antitumor activity of bispecific antibody-armed activated T cells derived from colorectal and pancreatic cancer patients. *Journal of Translational Medicine*, 2014 Jul 9;12:191
4. Al-Hajeli M, Asfar A, **Choi M**. Nab-paclitaxel: potential for the treatment of advanced pancreatic cancer. *Oncotarget and Therapy*, 2014 7:1-6.
5. Salem M, Jain N, Dyson G, **Choi M**, Shields AF, Critchfield J, Philip PA. Radiographic parameters in predicting outcome of patients with hepatocellular carcinoma treated with yttrium-90 microsphere radioembolization. *ISRN Oncology*, 2013 Sep 15;2013:538376. doi: 10.1155/2013/538376;PMID 24167742
6. Kim R, Mahipal A, **Choi M**, Saif MW. Biomarkers for pancreatic cancer: Is it ready for primetime? *Journal of Pancreas*, 2013 Jul 10;14(4):309-11. DOI: 10.6092/1590-8577/1676.
7. Tait L, Meyer J, McSpadden E, Cheng J, Baciewicz F, Meropol N, Cohen S, Wozniak A, **Choi M**, Konski A. Women at increased risk for cardiac toxicity following chemoradiation therapy for esophageal carcinoma. *Practical Radiation Oncology*, Oct 2013, Vol 3, Issue 4, Pages e149-e155.
8. Kim R, Tan A, **Choi M**, El-Rayes B. Geographic Differences in Approach To Advanced Gastric Cancer: Is There A Standard Approach? *Crit Rev Oncol Hematol*. 2013 Jun, 1040-8428(13)101-7.
9. Bang H, Littrup P, Currier B, Goodrich D, **Choi M**, Heilbrun L, Goodman A. Percutaneous Cryoablation of Metastatic Lesions from Colorectal Cancer: Efficacy and Feasibility with Survival and Cost-Effectiveness Observations. *ISRN Minimally Invasive Surgery*. 2012 Sept, Volume 2012, Article ID 942364. DOI: 10.5402/2012/942364.

Program Director/Principal Investigator (Last, First, Middle):

10. **Choi M**, Razzaque S, Kim R. Systemic Therapy of Advanced Pancreatic Cancer: Has the Landscape Changed? Clin Adv Hematol Oncol. 2012 Jul;10(7):442-51. PMID: 23262631
11. Azmi A, Banerjee S, Ali S, Wang Z, Bao B, Beck F, Maitah M, **Choi M**, Shields T, Philip P, Sarkar F, Mohammad R. Network Modeling of MDM2 inhibitor-Oxaliplatin Combination Reveals Biological Synergy in wt-p53 solid tumors. Oncotarget. 2011 May;2(5):378-392.
12. **Choi M**, Craft B, Geraci S. Surveillance and monitoring of adult cancer survivors. American Journal of Medicine. 124(7):598-601, 2011.
13. **Choi M.**, L. Heilbrun, R. Venkatramanamoorthy, Lawhorn-Crews JM, Zalupski MM, Shields AF. Using <sup>18</sup>F Fluorodeoxyglucose Positron Emission Tomography to Monitor Clinical Outcome in Patients Treated with Neoadjuvant Chemo-Radiotherapy for Locally Advanced Pancreatic Cancer. American Journal of Clinical Oncology. 2010 Jun;33(3):257-61.
14. Banerjee S, **Choi M**, Aboukameel Wang Z, Mohammad M, Chen J, Yang D, Sarkar FH, Mohammad RM. Preclinical studies of Apogossypolone, a novel pan inhibitor of Bcl-2 and Mcl-1 synergistically potentiates cytotoxic effect of gemcitabine in pancreatic cancer. Pancreas. 2010 Apr;39(3):323-31.
15. **M. Choi**, P. Jiang, L. Heilbrun, D. Smith, S. Gadgeel. Retrospective review of cancer patients age >80 years old treated with chemotherapy at a comprehensive cancer center. Critical Reviews in Oncology and Hematology. 2008 Sep;67(3):268-72.

#### D. Research Support

Merck (Investigator Initiated), "Prevention of Nausea and Vomiting Secondary to FOLFIRINOX Chemotherapy in GI Cancer Patients", \$62,648 (5/22/12 – present)

Xbiotech USA Inc : 2012-PT023 : 2013-014 : A Pivotal Phase III Study to Evaluate Overall Survival using MABp1 as a Monotherapy in Metastatic Colorectal Cancer Patients with Cachexia, \$ 44,434 (4/9/2013 – 8/2014)

Weill Cornell Medical College : 1208012946 : 2013-035 : An Open-Labeled, Multicenter Phase II Study of Cabazitaxel in Refractory Metastatic Gastric or Gastroesophageal Adenocarcinoma, \$45,000 (7/8/2013-8/2014)

Nordion, Inc., "A Phase III Clinical Trial Evaluating TheraSphere in Patients with Metastatic Colorectal Carcinoma of the Liver who have Failed First Line Chemotherapy", \$40,693 (5/22/12 – 5/21/15)

Nordion, Inc., "A Phase III Clinical Trial of Intra-arterial TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (HCC)", \$27,540 (6/21/12 – 6/20/15)

Myriad Genetics, Inc., "A Prospective, Randomized, Open-Label Trial Comparing OnDose® AUC Optimized 5-FU Based Administration versus Standard Body Surface Area (BSA) Dosing in Metastatic Colorectal Cancer Patients (mCRC) Treated with mFOLFOX6", \$44,467 (7/10/12 – 7/9/13)

Genentech, "A Phase II, Multicenter, Open-Label, Randomized Study Evaluating the Efficacy and Safety of FOLFIRI + MEHD7945A versus FOLFIRI + Cetuximab in Second Line in Patients with KRAS Wild-Type Metastatic Colorectal Cancer", \$189,659 (7/18/12 – 7/1/15)

Program Director/Principal Investigator (Last, First, Middle):

Kyowa Hakko Kirin Pharma, Inc., "Phase I/II Study of KRN330 plus Irinotecan after First-Line or Adjuvant FOLFOX/CapOx Failure in Patients with Metastatic Colorectal Cancer", \$125,152 (4/15/11 – 4/14/14)

Oncothyreon, Inc., "Phase 1/2 Study of PX-866 and Cetuximab", \$ 164,539 (10/11/11 – 10/10/2013)

Abbott Laboratories, "An Open-Label, Randomized Phase 3 Study of the Efficacy and Tolerability of Linifanib (ABT-869) vs Sorafenib in Subjects with Advanced Hepatocellular Carcinoma (HCC) (M10-963)", \$82,150 (2010 – 2011)

KCI, Immunotherapy Treatment of Advanced Colorectal and Pancreatic Cancer with anti-CD3 x anti-Erbitux Armed Activated T Cells (Phase Ib). Role: PI. \$60,000 10/8/11- 8/ 2014

Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Styliani-Anna (Stella) E. Tsirka	POSITION TITLE Professor of Pharmacological Sciences		
eRA COMMONS USER NAME (credential, e.g., agency login) stsirka			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Aristotle Univ of Thessaloniki, Greece	BSc	10/84	Chemistry
Aristotle Univ of Thessaloniki, Greece	PhD	01/89	Biochemistry

**A. Personal statement.** My laboratory explores the interactions and communications between the nervous and immune systems in physiological and pathological settings, such as glioma, stroke, epilepsy, multiple sclerosis. Many students and postdocs have worked over the years in these projects. I have been a member of the Molecular and Cellular Pharmacology (MCP/HBH) graduate program since 1998. Between 2003 and 2014 I served as the Director of the MCP/HBH Program. I have trained many graduate students in the Program as dissertation supervisor, and have served in numerous research advisory committees for students. I have mentored four MSTP students and serve on the committees of several others. Since the beginning of 2013 I also put together and direct the Stony Brook University Scholars in BioMedical Sciences program, which is based on the concepts of the HHMI Med-into-Grad programs, facilitating the exposure of graduate students in Life Sciences programs to translational clinical and medical science. I have also mentored several postdoctoral fellows and research scientists who have moved on to successful academic careers. My research has been funded by NIH and other funding sources. I have also been organizing and participating in ethics training for the MCP/HBH graduate students for many years. In addition to having been Graduate Program Director, I serve on the Admissions committee of the program and have participated in the program's recruitment efforts. I am certainly very committed to ensuring that we maintain and enhance the training environment of the MCP/HBH and MSTP programs, we recruit every year a group of smart, dedicated and diverse students, and help them develop into successful scientists in different scientific careers in academia, industry, policy and teaching.

**B. Positions and Honors.****Professional Positions**

1986-1989 Predoctoral Fellowship from IKY (The Greek Foundation of Fellowships)  
 1989- 1992 Postdoc fellow, Microbiology and Immunology, UCSF (Advisor: Dr. P. Coffino)  
 1992 Lecturer, Dept of Biochemistry, University of Athens, Greece  
 1993-1997 Postdoc Res. Associate, Pharmacology, SUNY Stony Brook, N.Y. (Advisor: Dr. S. Strickland)  
 1993 NIH-NIDDKD Postdoctoral Award  
 1994-1995 IHFSPO Postdoctoral Award  
 1998- 2000 Res. Asst. Professor, Dept of Psychiatry, SUNY Stony Brook, NY  
 1998- Member of SUNY Stony Brook IACUC  
 1998-1999 Targeted Research Award, SUNY Stony Brook (Neurological Disease)  
 2002- 2004 Carol M. Baldwin Breast Cancer Research Award  
 2000- 2003 Assistant Professor, Dept of Pharmacological Sciences, SUNY Stony Brook, NY  
 2003- 2014 Director, Molecular and Cellular Pharmacology Graduate Program, SUNY Stony Brook, NY  
 2004- 2008 Associate Professor, Dept of Pharmacological Sciences, SUNY Stony Brook, NY  
 2004 - 2010 Scientific advisory board of National Parkinson Foundation  
 2006- 2010 Established Investigator Award of the American Heart Association (National)  
 2007- 2010 Dean's Leadership Advisory Group

Program Director/Principal Investigator (Last, First, Middle):

- 2007 Dean's award for excellence in service to Graduate Education by a graduate program director  
 2008 - Professor, Dept of Pharmacological Sciences, SUNY Stony Brook, NY  
 2011 - Chair, Stony Brook University IACUC  
 2011 - President, Stony Brook University Hellenic Studies Center  
 2012 - Director of Stony Brook University Scholars in BioMedical Sciences (Med-into-Grad) Program

**Study Sections:** Grant Reviewer for Alzheimer's Association (2002-present); AHA-EIA (2011); NIH/NSC-C (2004); NIH/NST2 (2005-2009); NIH/SRB-M (2006); NIH/BDCN-90L/BINP (2004-2010, 2011); ZHD1 DRG-D (2011); AHA-Brain 1 (2007-); NIH-TWDA (2014-); NSF-GRFP (2014-)

1. S.E. Tsirka, A. Gualandris, D.G. Amaral, S. Strickland (1995) Excitotoxin-induced neuronal degeneration and seizure are mediated by tissue-type plasminogen activator. *Nature* 377:340-344.
2. Y.-P. Wu, C.-J. Siao, W. Lu, T.-C. Sung, M.A. Frohman, P. Milev, T.H. Bugge, J.L. Degen, J.M. Levine, R.U. Margolis, S.E. Tsirka. (2000) The tPA/plasmin extracellular proteolytic system regulates hippocampal mossy fiber reorganization through a novel proteoglycan substrate. *J. Cell Biol.* 148:1295-1304
3. M.M. Siddiq, and S.E. Tsirka. (2004) Tissue plasminogen activator and zinc are reciprocal antagonists of neurotoxicity. *Mol. Cell. Neurosci.* 25:162-171.
4. Emmetsberger J, Mirrione MM, Zhou C, Siddiq M, Fernandez-Monreal M, Ji K, SE Tsirka (2010) Tissue Plasminogen Activator alters intracellular sequestration of zinc through interaction with the transporter ZIP4, *J. Neurosci.* 30(19):6538-47 PMID: PMC2872103
5. Ji K, Akgul G, Wollmuth LP, Tsirka SE. (2013) Microglia actively regulate the number of functional synapses. *PLoS One*.8(2):e56293.
6. Nissen JC, Selwood D, Tsirka SE (2013) Tuftsin signals through its receptor neuropilin-1 via the transforming growth factor beta pathway. *J Neurochem*, 127(3):394-402.
7. Abraham AB, Bronstein R, Reddy AS, Maletic-Savatic M, Aguirre A, Tsirka SE. (2013) Aberrant Neural Stem Cell Proliferation and Increased Adult Neurogenesis in Mice Lacking Chromatin Protein HMGB2. *PLoS One*. 8(12):e84838.
8. Yao Y, Tsirka SE. (2011) Mouse MCP1 C-terminus inhibits human MCP1-induced chemotaxis and BBB compromise. *J Neurochem*. 118(2):215-23. PMID: PMC3129361

#### Additional publications relevant to the field

9. S.E. Tsirka, A.D. Rogove, S. Strickland (1996) Tissue plasminogen activator and neuronal cell death. *Nature* 384:123-124.
10. A.D. Rogove, S.E. Tsirka. (1998) Neurotoxic responses by microglia elicited by excitotoxic injury in the mouse hippocampus. *Curr.Biol.*8: 19-25.
11. Yao Y and Tsirka SE. Removal of the C-terminal domain of MCP1 by plasmin allows for the formation of a potent chemokine gradient (2010) *J. Biol. Chem*, 285(41):31509-16. PMID: PMC2951225
12. Sierra A, Encinas JM, Deudero JJP, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Tsirka SE, Maletic-Savatic M (2010) Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell*, 7:483-95 NIHMS233563
13. Talos F, Abraham A, Vaseva A, Holembowski L, Tsirka SE, Scheel A, Bode D, Dobbelsstein M, Bruck W, Moll UM (2010) p73 is an Essential Regulator of Neural Stem Cell Maintenance in Embryonal and Adult CNS Neurogenesis. *Cell Death Diff*, 17:1816-29 NIHMS263398
14. Bukhari N, Torres L and Tsirka SE. (2011) Axonal Repair in Spinal Cord Injury via Chondroitinase and the Tissue Plasminogen Activator (tPA)/Plasmin System, *J. Neurosci*, 31(42):14931-43. NIHMS333768.
15. Vaseva, AV, Holzmann, S, Ji, K, Tsirka, SE and Moll, UM (2012) p53 protein regulates the mitochondrial permeability transition pore during oxidative stress-induced necrosis and ischemic stroke. *Cell*, 149(7):1536-48

#### D. Research Support

Active

Program Director/Principal Investigator (Last, First, Middle):

2014-19 NASA: Remote, In Situ and Synchrotron Studies for Science and Exploration (RIS<sup>4</sup>E) PI: Glotch, (Role: Co-I, \$25K/year)

2014-2017 NIH-IRACDA: postdoctoral fellowship for Jillian Nissen (\$45K/year)

2013-2015: SUNYRF Reach: Pilot grant, effects of minocycline and NAC on microglia. PIs: Bergold, Feltri, Tsirka (\$25K)

2014-2016 "Evaluation of the effectiveness of a specially formulated hydrogel to prevent tissue adhesions after surgical intervention". PI: Tsirka (\$40K/year, Targeted Research Opportunities, SBU)

2014-2017 Institutionally-awarded research funds. PI: Tsirka (\$98K/year, SBU)

#### Completed

2012-2014 AHA predoctoral fellowship for Robert Bronstein

2012-2014 Turner predoctoral dissertation fellowship for Luisa Torres

2013-2014: SUNYRF Reach: Pilot collaborative grant assessing the effects of minocycline and NAC on microglia. PIs: Bergold, Feltri, Tsirka

2007-2013 NIH R01NS42168 Microglial effector pathways, PI: Tsirka

2012-2013 NMSS Modulation of T Cell Responses by Microglia During Experiments Allergic Encephalomyelitis (EAE) PI: Tsirka

2007-2012 NMSS, Center Grant from National Multiple Sclerosis Society, (with CoPIs Drs Levine, Colognato, Maletic-Savatic, and van Nostrand)

#### Pending

NIH R01: Role of Phospholipase D3 in late-onset Alzheimer's Disease. PIs: Frohman, Tsirka, van Nostrand

NIH R21: Modulation of neuronal activity by microglia. PIs: Tsirka, Wollmuth

NIH R01: Neurogenesis after stroke - the role of microglia. PI: Tsirka

#### Non Research / Graduate Training

NIH T32 GM0075186 Training Grant in Pharmacological Sciences (Principal Investigator: Styliani-Anna E. Tsirka)

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Powers, Robert Scott

eRA COMMONS USER NAME (credential, e.g., agency login): powerss

POSITION TITLE: Professor of Pathology and Director of Clinical Cancer Genomics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Carleton College, Minnesota	B.A.	05/1974	Mathematics
Columbia University, New York	Ph.D.	03/1983	Biological Sciences
Cold Spring Harbor Laboratory, New York	Postdoctoral	12/1985	Molecular Biology

**A. Personal Statement**

My role in this proposal will be to serve as a research mentor for the Scholars in BioMedical Sciences in Cancer Health Disparities. As a close colleague of Drs. McCombie and Tuveson at Cold Spring Harbor Laboratory, I believe that I can facilitate future development of translational projects involving both SUNY and CSHL for graduate students seeking further training in translational research.

I have been performing cancer genomics research since 1995. My main focus has been to use genome-wide DNA copy number profiling to identify recurrent amplified driver genes and to perform in vitro and in vivo analysis to validate their functional role in oncogenesis. My discoveries in this area include gene amplification of *PPM1D* and *ACK1* in breast and prostate adenocarcinomas and more recently activation of *FGF19* and *POFUT1* by genomic amplification and overexpression in hepatocellular carcinoma. I have experience in building collaborative research teams and am the PI of a multiple investigator NCI-funded Cancer Target Discovery and Validation Center (<http://ocg.cancer.gov/programs/ctd2>). This center continues to develop and apply methods to discover oncogenic drivers and dependencies based on analysis of human cancer genome data. In addition to copy number alterations in cancer, I have applied genome-wide methods to the study of mutational changes, epigenetic changes, and tumor-stromal interactions.

**B. Positions and Honors****Positions and Employment**

1974-1976	Computer Programmer, General Electric Co., NY
1977-1982	Graduate Research Assistant, Dept. of Biological Sciences, Columbia University
1982-1985	Postdoctoral Fellow, Cold Spring Harbor Laboratory, NY
1986-1988	Staff Investigator, Cold Spring Harbor Laboratory, NY
1988-1992	Assistant/Associate Professor, Dept. of Biochemistry, Robert Wood Johnson Medical School
1992-1995	Senior Scientist, Onyx Pharmaceuticals, CA
1995-2004	Scientific Director, Amplicon/Tularik Genomics Division, NY
1995-2004	Adjunct Associate Professor, Cold Spring Harbor Laboratory, NY
2004- 2014	Director, Human Cancer Genome Center & Associate Professor, CSHL
May 1 2014	Research Professor, Cold Spring Harbor Laboratory
May 1 2014	Professor, Department of Pathology, Stony Brook University, NY
May 1 2014	Director, Cancer Genomics, Cancer Center, Stony Brook University, NY

## **Honors and Professional Memberships**

1982-1985	Postdoctoral Fellowship Award, Leukemia Society of America
1988-1992	Editorial Board, Molecular and Cellular Biology
1989	Basil O'Conner Award
1992	A.C.S. Study Section (Molecular Biology)
2007	NCI Molecular Biology Program Project Study Section
2006-2013	NCI Cancer Genetics Study Section
2010-	Scientific Advisory Board, Hope Funds for Cancer Research
2014-	Chair, NCI Cancer Genetics Study Section

## **C. Contributions to Science**

1. **Identification and characterization of evolutionarily conserved genes in the RAS pathway.** I initiated the yeast *RAS* project as a postdoctoral fellow at Cold Spring Harbor in 1983, and continued these studies as an independent investigator through 1995. Although the downstream biochemical effector of RAS proteins was not conserved (adenyl cyclase in yeast, RAF and others in mammalian cells), the upstream activator CDC25 and the enzymes responsible for protein prenylation were highly conserved. Their discovery and study in yeast contributed to understanding their function in all eukaryotes.
  - a. Powers S, Kataoka T, Fasano O, Goldfarb M, Strathern J, Broach J, Wigler M. (1984) Genes in *S. cerevisiae* encoding proteins with domains homologous to the mammalian ras proteins. *Cell*.**36**:607-12.
  - b. Powers S, Michaelis S, Broek D, Santa Anna S, Field J, Herskowitz I, Wigler M. (1986) RAM, a gene of yeast required for a functional modification of RAS proteins and for production of mating pheromone a-factor. *Cell*.**47**:413-22.
  - c. He B, Chen P, Chen SY, Vancura KL, Michaelis S, Powers S. (1991) RAM2, an essential gene of yeast, and RAM1 encode the two polypeptide components of the farnesyltransferase that prenylates a-factor and Ras proteins. *Proc Natl Acad Sci U S A*.**88**:11373-7.
  - d. Lai CC, Boguski M, Broek D, Powers S. (1993) Influence of guanine nucleotides on complex formation between Ras and CDC25 proteins. *Mol Cell Biol*.**13**:1345-52.
2. **Developed and implemented methods that integrate genomic and functional analysis to identify and validate amplified driver genes in cancer.** In the early 2000s, my lab pioneered the oncogene discovery approach of using genome-wide DNA copy number profiling technologies (e.g. RDA, array CGH) together with mapping amplicon epicenters, expression analysis, and functional tests both in vitro and in vivo for oncogenic activity. Unlike other target discoveries in preclinical cancer research, all of our amplified oncogene discoveries have been independently validated.
  - a. Li J, Yang Y, Peng Y, Austin RJ, van Eyndhoven WG, Nguyen KC, Gabriele T, McCurrach ME, Marks JR, Hoey T, Lowe SW, Powers S. (2002) Oncogenic properties of PPM1D located within a breast cancer amplification epicenter at 17q23. *Nat Genet*.**31**:133-4.
  - b. Pei L, Peng Y, Yang Y, Ling XB, Van Eyndhoven WG, Nguyen KC, Rubin M, Hoey T, Powers S, Li J. (2002) PRC17, a novel oncogene encoding a Rab GTPase-activating protein, is amplified in prostate cancer. *Cancer Res*.**62**:5420-4.
  - c. Mu D, Chen L, Zhang X, See LH, Koch CM, Yen C, Tong JJ, Spiegel L, Nguyen KCQ, Servoss A, Peng Y, Pei L, Marks JR, Lowe SW, Hoey T, Jan LY, McCombie WR, Wigler MH, Powers S (2003) Genomic amplification and oncogenic properties of the KCNK9 potassium channel gene. *Cancer Cell*.**3**:297-302.
  - d. van der Horst EH, Degenhardt YY, Strelow A, Slavin A, Chinn L, Orf J, Rong M, Li S, See LH, Nguyen KQ, Hoey T, Wesche H, Powers S. (2005) Metastatic properties and genomic amplification of the tyrosine kinase gene ACK1. *Proc Natl Acad Sci U S A*.**102**:15901-6. PMID 1276100
3. **Focal copy number alterations contain multiple and interacting driver genes.** The paradigm for over 15 years has been that focal copy number alterations, particularly amplicons, have a single driver gene. Scott Lowe and I were the first to discover that focal amplicons can contain two driver genes (*YAP* and *BIRC2/IAP1*). Subsequently, my lab went on to show that one of the most common lung cancer amplicons at 14q13 contains three driver genes, *NKX2-1*, *NKX2-8*, and *PAX9*. Furthermore, we showed that these

three driver genes act synergistically in oncogenic assays. We also found that *FGF19*, only 50 kb distal to *CCND1*, is a co-driver gene of the 11q13 amplicon in liver cancer, and that these two genes functionally interacted in that *FGF19* controlled *CCND1* expression. It is now well established that most focal amplicons contain multiple driver genes, but the importance of functional interaction of multiple driver genes is still largely unappreciated.

- a. Zender L, Spector MS, Xue W, Flemming P, Cordon-Cardo C, Silke J, Fan ST, Luk JM, Wigler M, Hannon GJ, Mu D, Lucito R, Powers S, Lowe SW. (2006) Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. *Cell*.**125**:1253-67. PMID 3026384
- b. Kendall J, Liu Q, Bakleh A, Krasnitz A, Nguyen KC, Lakshmi B, Gerald WL, Powers S, Mu D. (2007) Oncogenic cooperation and coamplification of developmental transcription factor genes in lung cancer. *Proc Natl Acad Sci U S A*.**104**:16663-8. PMID 2034240
- c. Sawey ET, Chanrion M, Cai C, Wu G, Zhang J, Zender L, Zhao A, Busuttil RW, Yee H, Stein L, French DM, Finn RS, Lowe SW, Powers S. (2011) Identification of a therapeutic strategy targeting amplified *FGF19* in liver cancer by Oncogenomic screening. *Cancer Cell*.**19**:347-58. PMID 3061399

**4. Discovery of a targeted therapeutic strategy for *FGF19*-amplified hepatocellular carcinomas.** My lab discovered that amplification and overexpression in hepatocellular carcinomas of *FGF19*, encoding a secreted peptide that is a hepatocyte-specific mitogen, confers a strong selective Fgf19 signaling dependency. This suggested a targeted therapeutic strategy where hepatocellular carcinomas harboring *FGF19* amplification (approximately 15%) be treated with antibody inhibitors of Fgf19. Although the original anti-Fgf19 monoclonal antibody developed by Genentech that we studied was subsequently found to have unacceptable toxicity, two pharmaceutical companies have since then developed inhibitors of Fgf19's receptor (Fgfr4) that are less toxic and one, based on our study and validation by independent laboratories, is proceeding with clinical trials in HCC using *FGF19* amplification as a selective biomarker.

- a. Sawey ET, Chanrion M, Cai C, Wu G, Zhang J, Zender L, Zhao A, Busuttil RW, Yee H, Stein L, French DM, Finn RS, Lowe SW, Powers S. (2011) Identification of a therapeutic strategy targeting amplified *FGF19* in liver cancer by Oncogenomic screening. *Cancer Cell*.**19**:347-58. PMID 3061399

#### Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40132415/?sort=date&direction=ascending>

#### D. Research Support

##### Ongoing Research Support

U01CA168409 NIH (Powers) Role: PI 05/1/12-04/30/17

Computational and functional approaches to validating cancer genome targets.

Goal: Computationally analyze cancer genome data to guide functional screening of candidate oncogenic drivers and dependencies in model systems.

##### Completed Research Support

U01CA168409 NIH (Sander) Role: Co-investigator 05/01/12-04/30/14

Supplement for Computational and Functional Approaches to Validating Cancer Genome Targets.

Goal: Develop Dashboard (Web Interface) to Display CTD2 Data

R01CA124648 NIH (Powers) Role: PI 12/1/06-11/30/12

An integrative approach to cancer gene discovery in hepatocellular carcinoma

Goal: Use comparative genomics of human and mouse liver cancer to discover driver genes.

P01 CA013106 NIH (Hannon) Role: Core Director 02/10/05-12/31/13

CSHL Tumor Virus Grant YR 41 Genome & Proteomics Core D

Goal: Directing the Genome & Proteomics facility of the DNA Tumor Virus grant.

RC2CA148532-02 NIH (Powers) Role: PI 09/29/09-08/31/12

### CSHL Molecular Target Discovery and Development Center

This center uses informatic analysis of TCGA data coupled to functional tests in transplantable mouse models to discover new driver genes that underlie the diversity of genomic alterations found in human cancer.

U01CA105388      NIH (Lowe)      Role: Co-investigator      09/1/09-08/31/14

Identifying driver mutations and tumor dependencies by comparative oncogenomics.

Goal: Use oncogenomic screening in mouse models to discover oncogenes and tumor suppressor genes that drive human cancer development and to use synthetic lethal RNAi screens to discover tumor dependencies.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Lina M. Obeid</b>	POSITION TITLE <b>Professor</b>		
eRA COMMONS USER NAME (credential, e.g., agency login) <b>obeidl</b>			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Rutgers University, Piscataway, NJ	B.S.	1978	Chemistry
American University Beirut, Lebanon	M.D	1983	Medicine
Duke University, Durham, NC	Residency	1983-1987	Internal Medicine
Duke University, Durham, NC	Fellow	1988-1990	Endocrinology

**NOTE: The Biographical Sketch may not exceed four pages.**

**A. Personal Statement**

I have the expertise, leadership and motivation necessary to successfully carry out my role as a mentor on this grant application. I have a broad background in Medicine, biochemistry, cell and molecular biology with specific training and expertise in bioactive sphingolipid metabolism and role in cell regulation. In my medical training I gained significant expertise in pathophysiology of disease. As a postdoctoral fellow, I carried out biochemical and molecular and cellular biology studies on G-protein coupled receptors and protein kinase C. As an Assistant and Associate professor at Duke University, I established my research program to investigate the metabolism and role of bioactive lipid mediators in cell regulation, apoptosis and senescence. For the last decade as a Professor in Medicine, Biochemistry and Molecular Biology, I have consolidated my research program and expanded my studies into the role and regulation of bioactive lipids in disease pathobiology with a focus on inflammation, cancer and aging. As PI on several previous VA and NIH-funded grants, I successfully administered the projects and collaborated with other researchers. As a result of these previous experiences, I am aware of the importance of collaboration and communication in science, and of the value of shared instrumentation.

Moreover, through out my career I have been involved in the clinical training of medical students and residents, as well as, the research training of numerous students (in my laboratory and served on thesis advisory committee), post doctoral fellows, and junior faculty. Most of my trainees are in academic positions ranging from assistant and associate professors, staff scientists, and research fellows. I also have significant experience in teaching both in a didactic and in a non-classroom environment. In addition for over 5 years I was Associate Director of the NIH-funded MUSC Medical Scientist Training Program (MSTP), and for the last 10 years I served as PI on a Center of Biomedical Research Excellence (COBRE) in Lipidomics and Pathobiology. All of this extensive experience in training at multiple academic levels has prepared me to have a leadership role as a mentor on this proposal.

In summary, I have a demonstrated record of successful and productive research projects in an area of high relevance for disease, and my expertise and experience have prepared me to lead research projects and to be a mentor for more junior scientists at all levels.

**B. Positions and Honors**

1990 - 1992	Associate, Department of Medicine, Duke University
1990 - 1998	Staff Physician Durham Veterans Affairs Medical Center
1992 - 1996	Assistant Professor, Department of Medicine, Duke University
1994 - 1998	Assistant Professor, Department of Cell Biology, Duke University
1996 - 1998	Associate Professor: Department of Medicine, Duke University
1998 - 2012	Staff Physician Ralph H Johnson Veterans affairs Medical Center
1998 - 2012	Boyle Professor of Medicine, Department of Medicine, Medical University of South Carolina

1998 - 2012 Professor, Department of Biochemistry, Medical University of South Carolina  
 2002 - 2011 Associate Director for Aging Biology, Center of Aging, Medical University of South Carolina  
 2002 - 2011 Associate Director, Medical Scientist Training Program, Medical University of South Carolina  
 2012 - Professor of Medicine, Stony Brook University  
 2012 - Dean for Research, Stony Brook University  
 2012- Staff Physician Northport Veterans Affairs Medical Center

**Honors and Awards:** B.S. with honors 1978; Dean's honor list, School of Medicine 1978-83; Member, Alpha Omega Alpha, Honor Medical Society 1982; M.D. with distinction from American University of Beirut, School of Medicine 1983; Hartford Scholar 1989-90; Henry Christian Memorial Award 1990; Clinical Investigator Award, National Institute of Aging 1992-97; James A. Shannon Director's Award 1994-96; Paul Beeson Physician Faculty Scholar 1995-98; First Award, National Institute of Aging 1995-00; Veterans Affairs Merit Award 2000-present; 2002 Elected to membership of Association of American Physicians; AAAS Fellow (2004). JLR lectureship awardee for the FASEB lysophospholipid meeting, august 2013.

**Study Sections:** Veteran's Administration (Ad hoc reviewer); National Science Foundation Ad hoc reviewer; American Federation of Aging Research (Beeson Program, Scientific Advisory Board, 1999 - 2005); American Federation of Aging Research (AFAR) Research Committee Review board (2003-present); AFAR (Atlanta Affiliate, 2003 - present); National Cancer Institute (NCI)-Special Panel for PPG, 1999 & 2001; National Cancer Institute (NCI) Special Panel for RFA CA00-002, 2000; NIH: Permanent Member of Medical Biochemistry then Physiological Chemistry study sections, 2001 – 2005. NIH:Special Emphasis Panel/Scientific Review Group ZRG1 BCMB-S (02) M 2011. NCI Special Emphasis Panel – Provocative Question B, 2013. RFA RM-11016: Regional Comprehensive Metabolomics Resource Cores ZRG1 BST-F (50) R, 2013.

### C. Selected Peer-reviewed Publications (pubs selected from recent pubs and out of ~200 total)

1. Johnson, K.R., Johnson, K.Y., Crellin, H.G., Ogretmen, B., Boylan, A.M., Harley, R.A., and **Obeid, L.M.** (2005) Immunohistochemical Distribution of Sphingosine Kinase 1 in Normal and Tumor Lung Tissue. *JHC* 53(9): 1159-1166.
2. Taha, T.A., Kitatani, K., El-Alwani, M., Bielawski, J., Hannun, Y.A., and **Obeid, L.M.** (2006) Loss of sphingosine kinase-1 activates the intrinsic pathway of programmed cell death: modulation of sphingolipid levels and the induction of apoptosis. *FASEB* 20(3):482-4.
3. Spassieva, S., Bielawski, J., Anelli, V., and **Obeid, L.M.** (2007) Chapter 12: Combination of C17 Sphingoid Base Homologues and Mass Spectrometry Analysis as a New Approach to Study Sphingolipid Metabolism. In *Methods Enzymology*. Volume 434 Lipidomics and Bioactive Lipids: Lipids and Cell Signaling, Brown, H.A (Ed.) ISBN: 978-0-12-373965-0.
4. Anelli, V., Gault, C.R., Cheng, A.B., and **Obeid, L.M.** (2008) Sphingosine Kinase 1 is Up-regulated During Hypoxia in U87MG Glioma Cells: Role of Hypoxia-inducible Factors 1 and 2. *J Biol Chem.* FEB 8; 283(6): 3365-75. **\*PMCID Not applicable to this publication.**
5. Hannun, Y.A., and **Obeid, L.M.** (2008) Principles of bioactive lipid signaling: lessons from sphingolipids. *Nature Reviews Molecular Cell Biology*. Feb 9; (2):139-50. **\*PMCID Not applicable to this publication.**
6. Hammad, S., Crellin, H., Wu, X., Melton, J., Anelli, V., and **Obeid, L.M.** (2008) Dual and Distinct Roles for Sphingosine Kinase 1 and Sphingosine 1 Phosphate in the Response to Inflammatory Stimuli in RAW Macrophages. *POLM*. Mar; 85(3-4):107-14. **PMCID: PMC2290737**
7. Novgorodov, S.A., Gudiz, T.I., **Obeid, L.M.** (2008). Long-Chain Ceramide Is A Potent Inhibitor of the Mitochondrial Permeability Transition Pore. *J Biol Chem.*, Sep 5; 283(36):24707-17. **PMCID: PMC2529003**

8. Snider, A.J., Kawamori, T., Bradshaw, S.G., Orr, K.A., Gilkeson, G., Hannun, Y.A., and **Obeid, L.M.** (2009) A Role For Sphingosine Kinase 1 in Dextran Sulfate Sodium-Induced Colitis. *FASEB* Jan; 23(1):143-52. **PMCID: PMC2626622**

9. Kawamori, T., Kaneshiro, T., Okumura, M., Maalouf, S., Uflacker, A., Bielawski, J., Hannun Y.A., **Obeid L.M.** (2009) Role for sphingosine kinase 1 in colon carcinogenesis. *FASEB* Feb; 23(2):405-14. **PMCID: PMC2630788**

10. Spassieva, S.D., Mullen, T.D., Townsend, D.M., and **Obeid, L.M.** (2009) Disruption of ceramide synthesis by CerS2 down-regulation leads to autophagy and the unfolded protein response. *Biochem. J.* 2009 Sep 3. **PMCID: PMC19728861**

11. Siskind LJ, Mullen TD, Rosales KR, Clarke CJ, Hernandez-Corbacho MJ, Edinger AL, **Obeid LM.** The BCL-2 protein BAK is required for long-chain ceramide generation during apoptosis. *J Biol Chem.* 2010 Feb 18. [Epub ahead of print] PMID: 20172858. **PMCID: PMC2825918.**

12. Heffernan-Stroud LA, **Obeid LM.** p53 and regulation of bioactive sphingolipids. *Adv Enzyme Regul.* 2011;51(1):219-28. **PMCID:PMC3078951**

13. Heffernan-Stroud, L. A., Helke, K.L., Jenkins, R.W., DeCosta, A.M., Hannun, Y.A., and **Obeid, L.M.** (2011) Defining a role for sphingosine kinase 1 in p53-dependent tumors. *Oncogene.* 2012 Mar 1;31(9):1166-75. doi: 10.1038/onc.2011.302. Epub 2011 Jul 18. **PMCID:PMC3278571**

14. Chipuk JE, McStay GP, Bharti A, Kuwana T, Clarke CJ, Siskind LJ, Obeid LM, Green DR. (2012) Sphingolipid metabolism cooperates with BAK and BAX to promote the mitochondrial pathway of apoptosis. *Cell.* 2012 Mar 2;148(5):988-1000. **PMID: 22385963**

15. Snider AJ, Wu BX, Jenkins RW, Sticca JA, Kawamori T, Hannun YA, **Obeid LM.** Loss of neutral ceramidase increases inflammation in a mouse model of inflammatory bowel disease. *Prostaglandins Other Lipid Mediat.* 2012 Dec;99(3-4):124-30. doi: 10.1016/j. prostaglandins 2012.08.003. Epub 2012 Aug 31.

16. Gault CR, Eblen ST, Neumann CA, Hannun YA, **Obeid LM .** Oncogenic K-Ras regulates bioactive sphingolipids in a sphingosine kinase 1-dependent manner. *J Biol Chem.* 2012 Sep 14;287(38):31794-803. **PMCID: PMC3442513**

17. Gandy KA, Canals D, Adada M, Wada M, Roddy P, Snider AJ, Hannun YA, **Obeid LM.** Sphingosine 1-phosphate induces filopodia formation through S1PR2 activation of ERM proteins. *Biochem J.* 2013 Feb 1;449(3):661-72. doi: 10.1042/BJ20120213. PMID: 23106337

18. Orr Gandy KA, Adada M, Canals D, Carroll B, Roddy P, Hannun YA, **Obeid LM.** Epidermal growth factor-induced cellular invasion requires sphingosine-1-phosphate/sphingosine-1-phosphate 2 receptor-mediated ezrin activation. *FASEB J.* 2013 Apr 29.

## D. Research Support

### Ongoing

1) Merit Award (Obeid - PI) 10/1/10 - 09/30/2017

Agency: Veteran's Administration

"Bioactive Sphingolipid enzymes as targets in inflammation"

The long-term goal of this project is to define the role of ceramidases and sphingosine kinase in inflammation and to target these enzymes for novel anti-inflammatory therapy.

2) 9R01GM097741-13A1 (Obeid - PI) 3/1/12-5/31/15

Agency: NIGMS (The competing renewal of this grant scored in the 13th% and is expected to be funded)  
Role and Regulation of Ceramide Synthases in Apoptosis

The aims of this proposal is to dissect the role of the novel family of Ceramide Synthases in regulation of specific and distinct pools of ceramide and their role in apoptosis. Moreover this proposal will dissect the role of Bak in regulation of ceramide metabolism.

3) P01 CA097132-11 (Hannun – PI, Obeid - Project 3 Leader)  
09/01/014-08/31/19

Agency: NIH/NCI  
Sphingolipids in Cancer Biology and Therapy

The aims of this proposal are to study the role of sphingosine kinase in p53 null and mutant cancer development.

## Completed

1) P20 RR17677 (Obeid - PI) 09/26/02 - 04/1/12

Agency: NIH/NCRR

"COBRE in Lipidomics and Pathobiology"

To develop an interactive Center of Lipidomics and Pathobiology that will promote the growth and excellence of research at MUSC. This involves mentoring 5 junior investigators in their respective projects in the area of lipidomics and pathology, as well as three cores.

2) P30 CA138313-01 (Kraft - PI) 04/1/09-03/31/14

Agency: NIH/NCI

Medical University of South Carolina-Cancer Center Support Grant

Leader of Program Lipid signaling in cancer

Major goal: To support the ongoing research infrastructure, research programs, shared resources, developmental funds, and administration of the Hollings Cancer Center at the Medical University of South Carolina to ensure the development of more effective approaches to cancer prevention, diagnosis, and therapy.

3) IR01-GM-62887 (Obeid - PI) 5/01/01 – 8/31/11

Agency: NIH/NIA

"Sphingosine Phosphate in Inflammation"

The main goals of this proposal were focused on the role of sphingosine kinase 1 and sphingosine phosphate in inflammation.

4) 1R01-AG-16583 (Obeid - PI) 09/01/01-08/31/11

Agency: NIH/NIA

"Mitochondrial Ceramide in Chemotherapy-induced Apoptosis"

The long-term goal of this proposal is to develop ceramides as novel therapeutic approaches to cancer treatment. The sphingolipid ceramide has recently emerged as a key regulator of apoptosis in response to multiple inducers such as chemotherapeutic agents, UV radiation, and tumor necrosis factor alpha.

5) Merit Award (Obeid - PI) 01/1/04 - 12/31/08

Agency: Veteran's Administration

"Regulation of Human Alkaline Ceramidases and Role in Cancer Biology "

Specific aims of this grant are to clone two other human homologues of alkaline phytoCDase and determine their enzymatic function in cells and *in vitro*. To study the biochemical and cellular regulation of the two new putative alkaline CDases. To determine the differential regulation and role of the different alkaline CDases in regulation of apoptosis.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Hussain, M. Mahmood

POSITION TITLE: Professor

eRA COMMONS USER NAME (credential, e.g., agency login): mhussain

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Osmania University, Hyderabad, India	M. Sc.	1978	Biochemistry
University of Hyderabad, India	M. Phil.	1979	Intestinal absorption
Oklahoma State University, USA	Ph.D.	1984	Biochemistry
University of Copenhagen, Denmark	Lic. Med.	1986	Biochemistry

**A. Personal Statement**

I joined the Medical College of Pennsylvania as an Assistant Professor in 1991. Since then, my laboratory has been studying lipid absorption and lipoprotein assembly. My laboratory has developed several methods and models to study chylomicron assembly and secretion. We studied secretion of lipids with chylomicrons and showed that newly synthesized triglycerides are preferentially secreted with chylomicrons. We described mechanisms for the absorption and transport of vitamins A and E. We have shown that there are two pathways (apoB-dependent and -independent) involved in cholesterol absorption. Further, we have documented the importance of MTP, ABCA1, ACAT2, apoAI, and apoAIV in these pathways.

Since MTP is an essential chaperone for the assembly of chylomicrons, we have paid much attention to its role in lipoprotein assembly. We studied protein-protein interactions between apoB and MTP, demonstrated two independent functional domains that carry out lipid transfer and apoB binding activities in MTP, and discovered that binding of MTP to lipid vesicles enhances its binding with apoB. We showed that MTP was evolved as a phospholipid transfer protein and acquired triglyceride transfer activity during a transition from invertebrates to vertebrates. Also, provided molecular and biochemical explanations for some missense mutations found in abetalipoproteinemia subjects. We have developed new assays to measure MTP activity using fluorescent lipids. In addition, we showed that MTP transfers phospholipids onto CD1d. In short, I have a long history and demonstrated expertise to study MTP, lipid absorption, and lipoprotein assembly and secretion.

Recently, we revealed that lipid absorption is regulated by circadian rhythms and disruptions in these rhythms causes hyperlipidemia and enhances atherosclerosis in mice. We have also identified a novel regulator, *Ire1<sup>2</sup>*, of intestinal lipid absorption. We showed that *Ire1<sup>2</sup>* regulates MTP expression in the intestine involving post-transcriptional degradation of mRNA. Moreover, we have identified that microRNA-30c regulates lipoprotein production without causing steatosis. We showed overexpression of miR-30c in the livers of mice reduces plasma lipids and atherosclerosis suggesting that it might be a better agent than MTP inhibitors to reduce plasma lipids.

Over the years, I have published 106 peer-reviewed papers and 38 reviews. I have served as the principal investigator on several NIH and AHA grants over the past 25 years. I have managed research groups consisting of visiting scientists (10), clinical fellows (9), junior faculty (3), postdoctoral fellows (17), graduate students (14, including 6 MD, PhD students), rotating students (21), under graduate students (18), and technicians (7), and have ample experience in hiring, training, safety, budget etc. Moreover, I have

collaborated with several national and international researchers and produced several peer-reviewed publications. Hence, I have demonstrated track-record and experience to lead the proposed project.

### **Positions:**

6/87-9/91 Staff Research Investigator, Gladstone Institute for Cardiovascular Disease, UCSF, CA  
 10/91-6/95 Assistant Professor, Pathology and Biochemistry, the Medical College of Pennsylvania  
 7/95-9/99 Associate Professor, MCP Hahnemann University, Philadelphia, PA  
 10/99-4/02 Associate Professor, SUNY Downstate Medical Center, Brooklyn, NY  
 4/02-present Professor, SUNY Downstate Medical Center, Brooklyn, NY  
 4/03-present President, Chylos, Inc., Woodbury, NY  
 09/13-present Research Scientist, VA New York Harbor Healthcare System, Brooklyn, NY  
 05/14-present Distinguished Professor, State University of New York, NY

**Other Experience and Professional Memberships:** Premium professional silver heart member, AHA, Dallas, TX (2005); Editorial board member, Journal of Lipid Research (2008-present); Co-Editor-in-Chief, Nutrition & Metabolism (London) (2004-2008), Editor-in-Chief, Nutrition & Metabolism (London) 2009-present; Editorial board member, Atherosclerosis, thrombosis, and vascular biology (2009-present);

**Grant review committees:** American Heart Association, Southeastern PA Affiliate (1995-1997); Northeast Consortia Peer Review Study Group 2, AHA (2000-2005); Ad hoc reviewer for the NIH: from 1999 to present; WHO Regional Office for Europe, Copenhagen, Denmark (2000); Member, Endocrinology Merit Review Subcommittee, VA (2004-2010); Vice Chair, NE2 Study Group, AHA (2004); Chairman, Northeast 2 Study Group, AHA (2005); AHA National Center (2007-2009); Medical research council, UK (2011); French national research agency (2012-present); Chair, NIH Study section ZDK1 GRB-N (2013);

**B. Honors:** National Merit Scholarship, Government of India (1976-1978); Danish International Development Fellow, Denmark (1980-1981); Boston University School of Medicine Research Award (1986); Irvine H. Page Award, Council on Arteriosclerosis, Thrombosis, and Vascular Biology, AHA (1998); Leonard N. Horowitz Research Award, AHA, Southeastern Pennsylvania Affiliate (1998); Established Investigator, AHA (1999-2002); Outstanding Achievement Award, International Journal of Oncology, Oncology Reports, International Journal of Molecular Medicine, Crete, Greece (2001); President, New York Lipid and Vascular Biology Research Club (2001-2002); Promising Inventor Award, The Research Foundation, SUNY, Albany, NY (2003); Chancellor's Research Recognition Award, The Research Foundation, State University of New York, Albany, NY (2003); Research administration volunteer research award, AHA, New Haven, CT (2005); Chancellor's award for excellence in scholarship and creative activities, Brooklyn, NY (2005); 2011 ATVB Special Recognition Award in Arteriosclerosis, American Heart Association, National Center

**C. Contribution to Science:** Different topics investigated and representative publications in each area are listed below.

### **Involvement of bone marrow in chylomicron remnant catabolism:**

1. **Hussain MM**, Mahley RW, Boyles JK, Fainaru M, Brecht WJ, and Lindquist P (1989) Chylomicron/chylomicron remnant clearance by liver and bone marrow in rabbits: Factors that modify tissue-specific uptake. **J Biol Chem** 264:9571-9582.
2. Mahley RW, Weisgraber KH, **Hussain MM**, Greenman B, Fisher M, Vogel T, and Gorecki M (1989) Intravenous infusion of apolipoprotein E accelerates clearance of plasma lipoproteins in rabbits. **J Clin Invest** 83:2125-2130.
3. Anderson LJ, Boyles JK, and **Hussain MM** (1989) A rapid method for staining large chylomicrons. **J Lipid Res** 30:1819-1824.
4. **Hussain MM**, Mahley RW, Boyles JK, Lindquist PA, Brecht WJ, and Innerarity TL (1989) Chylomicron metabolism: Chylomicron uptake by bone marrow in different animal species. **J Biol Chem** 264:17931-17938.

### **Role of receptors and proteoglycans in chylomicron remnant clearance:**

1. **Hussain MM**, Maxfield FR, Mas-Oliva J, Tabas I, Ji ZS, Innerarity TL, and Mahley RW (1991) Clearance of chylomicron remnants by low density lipoprotein receptor-related/ $\pm_2$ -macroglobulin receptor. **J Biol Chem**

266:13936-13940.

2. Ji ZS, Brecht WJ, Miranda RD, **Hussain MM**, Innerarity TL, and Mahley RW (1993) Role of heparan sulfate proteoglycans in the binding and uptake of apolipoprotein E-enriched remnant lipoproteins by cultured cells. **J Biol. Chem** 268:10160-10167.
3. **Hussain MM**, Innerarity TL, Brecht WJ and Mahley RW (1995) Chylomicron metabolism in normal, cholesterol-fed and Watanabe heritable hyperlipidemic rabbits: Saturation of the sequestration step of the remnant clearance pathway. **J Biol Chem.** 270:8578-8587.
4. **Hussain MM**, Glodberg IJ, Weisgraber KH, Mahley RW, and Innerarity TL (1997) Uptake of chylomicrons by the liver, but not by the bone marrow, is modulated by lipoprotein lipase activity. **Arterioscl Thromb Vasc Biol** 17:1407-1413.

#### **Assembly and secretion of lipids with chylomicrons:**

1. Luchoomun J, and **Hussain MM** (1999) Assembly and secretion of chylomicrons by differentiated Caco-2 cells: nascent triglycerides and preformed phospholipids are preferentially used for lipoprotein assembly. **J Biol Chem** 274:19565-19572.
2. **Hussain MM**, Kancha RK, Zhou Z, Luchoomun J, Zu H, Bakillah A (1996) Chylomicron assembly and catabolism: role of apolipoproteins and receptors. **Biochim Biophys Acta** 1300:151-170.
3. **Hussain MM** (2000) A proposed model for the assembly of chylomicrons. **Atherosclerosis** 148:1-15
4. **Hussain MM**, Kedees MH, Singh K, Athar H, Jamali NZ (2001) Signposts in the assembly of chylomicrons. **Front Biosci** 6:D320-D331.

#### **Secretion of fat-soluble vitamins with chylomicrons:**

1. Nayak N, Harrison EH, and **Hussain MM** (2001) Retinyl ester secretion by the intestinal cells is a highly specific and regulated process that is dependent on the assembly and secretion of chylomicrons. **J Lipid Res** 42: 272-280.
2. During A, **Hussain M M**, Morel DW, and Harrison EH (2002) Carotenoid uptake and secretion by Caco-2 cells: <sup>2</sup>-carotene isomer selectivity and carotenoids interactions. **J Lipid Res** 43:1086-1095.
3. Anwar K, Kayden HJ, and **Hussain MM** (2006) Transport of vitamin E by differentiated Caco-2 cells. **J Lipid Res** 47:1261-1273. Epub 2006 Mar 28.
4. Anwar K, Iqbal J, and **Hussain MM** (2007) Mechanisms involved in Vitamin E transport by primary enterocytes and in-vivo absorption. **J Lipid Res** 48:2028-2038. Epub 2007 June 20.

#### **ApoB-dependent and apoB-independent pathways of lipid absorption:**

1. Iqbal J, Anwar K and **Hussain MM** (2003) Multiple, independently regulated pathways of cholesterol transport across the intestinal epithelial cells. **J Biol Chem** 278:31610-31620. Epub 2003 May 29.
2. Iqbal J, and **Hussain MM** (2005) Evidence for multiple complementary pathways for efficient cholesterol absorption in mice. **J Lipid Res** 46:1491-1501. Epub 2005 April 16.
3. Iqbal J, Parks, JS, **Hussain MM** (2013) Lipid absorption defects in intestine-specific microsomal triglyceride transfer protein and ATP-binding cassette transporter A1 deficient mice. **J Biol Chem** 288:30432-30444. Epub 2013 Sept 09.
4. Iqbal J, Boutjdir M, Rudel LL, **Hussain MM** (2014) Intestine specific MTP deficiency with global ACAT2 gene ablation lowers acute cholesterol absorption with chylomicrons and high density lipoproteins. **J Lipid Res.** 55:2261-2275. Epub 2014 Jul 16.

#### **Methods to measure apolipoproteins and MTP activity:**

1. Bakillah A, Zhou Z, Luchoomun J, and **Hussain MM** (1997) Measurement of apolipoprotein B in various cell lines: correlation between intracellular levels and rates of secretion. **Lipids** 32:1113-1118.
2. Athar H, Iqbal J, Jiang XC, and **Hussain MM** (2004) A simple, rapid and sensitive fluorescence assay for microsomal triglyceride transfer protein. **J Lipid Res** 45:764-772. Epub 2004 Feb 1.
3. Rava P, Athar H, Johnson C, and **Hussain MM** (2005) Transfer of cholesteryl esters and phospholipids as well as net deposition by microsomal triglyceride transfer protein. **J Lipid Res** 46:1779-1785. Epub 2005 May 16.

#### **Protein-protein interactions between apoB and MTP:**

1. **Hussain MM**, Bakillah A, and Jamil H (1997) Apolipoprotein B binding to microsomal triglyceride transfer protein decreases with increases in length and lipidation: implications in lipoprotein biosynthesis.

### **Biochemistry 36:13060-13067.**

2. Bakillah A, Jamil H, and **Hussain M M (1998)** Lysine and arginine residues in the N-terminal 18% of apolipoprotein B are critical for its binding to microsomal triglyceride transfer protein. **Biochemistry** 37:3727-3734.
3. **Hussain MM**, Bakillah A, Nayak N, and Shelness GS (1998) Amino acids 430-570 in apolipoprotein B are critical for its binding to microsomal triglyceride transfer protein. **J Biol Chem** 273:25612-25615.
4. Bakillah A, and **Hussain MM (2001)** Binding of microsomal triglyceride transfer protein to lipids results in increased affinity for apolipoprotein B: Evidence for stable microsomal MTP/lipid complexes. **J Biol Chem** 276:31466-31473. Epub 2001 Jun 26.

### **Role of MTP's phospholipid transfer activity in lipoprotein assembly and secretion:**

1. Rava P, Ojakian GK, Shelness GS and **Hussain MM (2006)** Phospholipid transfer activity of microsomal triglyceride transfer protein is sufficient for the assembly and secretion of apolipoprotein B lipoproteins. **J Biol Chem** 281:11019-11027. Epub 2006 Feb. 13.
2. Rava P, and **Hussain MM (2007)** Acquisition of triacylglycerol transfer activity by microsomal triglyceride transfer protein during evolution. **Biochemistry**. 46:12263-12274. Epub 2007 Oct 09. PMID: 17924655.
3. Khatun I, Zeissig S, Iqbal J, Wang M, Curiel D, Shelness GS, Blumberg RS, **Hussain MM (2012)** Phospholipid transfer activity of microsomal triglyceride transfer protein produces apolipoprotein B and reduces hepatosteatosis while maintaining low plasma lipids in mice. **Hepatology**, 55:1356-1368. Epub 2012 Mar 20.

### **Contribution to the role of MTP in CD1D and NKT cells:**

1. Dougan SK, Salas A, Rava P, Agyemang A, Kaser A, Morrison G, Khurana A, Kronenberg M, Johnson C, Exley M, **Hussain MM**, Blumberg RS (2005) Microsomal triglyceride transfer protein: lipidation and control of CD1d on antigen presenting cells. **J Exp Med** 202:529-539. Epub 2005 Aug. 08.
2. Dougan SK, Rava P, **Hussain MM**, Blumberg RS (2007) MTP regulated by an alternate promoter is essential for NKT cell development. **J Exp Med** 204:533-545. Epub 2007 Feb 20.
3. Zeissig S, Murata K, Sweet L, Publicover J, Hu Z, Kaser A, Bosse E, Iqbal J, **Hussain MM**, Balschun K, Rocken C, Arlt A, Gunther R, Hampe J, Schreiber S, Baron JL, Moody DB, Liang TJ, Blumberg RS (2012) Hepatitis B virus-induced lipid alterations contribute to natural killer T cell-dependent protective immunity. **Nat Med** 18:1060-1068. Epub 2012 June 17.

### **Regulation of chylomicron assembly and intestinal lipid absorption by IRE1<sup>2</sup>:**

1. Iqbal J, Dai K, Seimon T, Jungreis R, Oyadomari M, Kuriakose G, Ron D, Tabas I, and **Hussain MM (2008)** IRE1<sup>2</sup> inhibits chylomicron production by selectively degrading MTP mRNA. **Cell Metabolism** 7:445-455. PMID: 18460335.
2. Dai K, Khatun I, and **Hussain MM (2010)** NR2F1 and Ire1<sup>2</sup> suppress MTP expression and lipoprotein assembly in undifferentiated intestinal epithelia cells. **Arterioscl Thromb Vasc Biol** 30:568-574. PMID: 20007910.
3. Iqbal J, Queiroz J, Li Y, Jiang XC, Ron D, **Hussain MM (2012)** Increased intestinal lipid absorption caused by Ire1<sup>2</sup> deficiency contributes to hyperlipidemia and atherosclerosis in Apolipoprotein E-deficient mice. **Circ Res** 110:1575-1584. Epub 2012 May 3.
4. **Hussain MM**, Leung TM, Zhou L, Abu-Merhi S (2013) Regulating intestinal function to reduce atherogenic lipoproteins. **Clinical Lipidology** 8:481-490.

### **Circadian regulation of plasma lipids:**

1. Pan X, and **Hussain MM (2007)** Diurnal regulation of microsomal triglyceride transfer protein and plasma lipid levels. **J Biol Chem** 282:24707-24719. Epub 2007 June 15.
2. Pan X, and **Hussain MM (2009)** Clock is important for food and circadian regulation of macronutrient absorption in mice. **J Lipid Res** 50: 1800-1813. Epub 2009 Apr 22. PMID: 19387090.
3. Pan X, Zhang Y, Wang L, and **Hussain MM (2010)** Diurnal regulation of MTP and plasma lipid by Clock is mediated by SHP. **Cell Metabolism**. 12:174-186. Epub 2010 Aug 4. PMID: 20674862
4. Pan X, Jiang XC, **Hussain MM (2013)** Impaired cholesterol metabolism and enhanced atherosclerosis in Clock mutant mice. **Circulation** 128:1758-1769. Epub 2013 Sept 06.

### **MicroRNAs regulating plasma lipids and lipoproteins:**

1. Soh J, Iqbal J, Queiroz J, Fernandez-Hernando C, **Hussain MM (2013)** MicroRNA-30c reduces hyperlipidemia and atherosclerosis in mice by decreasing lipid synthesis and lipoprotein secretion. **Nat. Med.** 19:892-900. Epub 2013 June 9.
2. Soh J, **Hussain MM (2103)** Supplementary site interactions are critical for the regulation of microsomal triglyceride transfer protein by microRNA-30c. **Nutr Metab (Lond).** 10:56. Epub 2013 Sept 04.
3. Irani S, **Hussain MM (2015)** Role of microRNA-30c in lipid metabolism, adipogenesis, cardiac remodeling and cancer. **Curr Opin Lipidol** In press.

## D. Research Support

### Ongoing Research Support

“Avoiding toxicity associated with MTP ablation” The aims are to find ways to avoid toxicities associated with MTP inhibition in mice as well as to recognize mechanisms involved in the toxicity associated with MTP inhibition in mice. NIH/NHLBI 3RO1 HL095924-03; 02-01-2010 to 01-31-2014. There is no overlap with the current application. This grant is in no-cost extension and will not be renewed. PI: M. Mahmood Hussain.

“Circadian regulation of lipid metabolism” The aims are to study the role of Bmal1 in the diurnal and food-entrained regulation of plasma lipids. Agency: NIH/NIDDK, RO1 DK081879-02; 07-01-2011 to 08-31-2015. There is no overlap with the current application. PI: M. Mahmood Hussain.

“Regulation of plasma lipids and atherosclerosis by miR-30c” The aims are to understand how miR-30c modulates hyperlipidemia and atherosclerosis and explain mechanisms involved in reducing plasma lipids by miR-30c. Agency: VA Merit Award BX1728; 04-01-2013 to 06-30-2017. There is no overlap with the current application. PI: M. Mahmood Hussain.

“Exploration of lipid transport proteins as drug targets for the treatment of tuberculosis” The goal of this planning grant is to investigate the function and inhibition of lipid transport mechanisms in Mycobacterium tuberculosis, towards developing more effective anti-TB therapeutics. Agency: Health Now/SUNY Network of Excellence in Health; April 17, 2014 – August 31, 2015. There is no overlap with the current application. P.I. Jessica Seeliger; Co:PI: M. Mahmood Hussain.

“microRNA-30c mimics as potential therapeutic agents to lower plasma lipids & regress atherosclerosis”. The goal of this grant is to find out if miR-30c mimics curtail diet induced hyperlipidemia and atherosclerosis in western diet fed C57Bl6J and *Apoe*<sup>-/-</sup> mice. Agency: Technology Accelerator Fund Class 2014 Fund/Research Foundation of SUNY; September 08, 2014 – February 27, 2015. There is no overlap with the current application. PI: M. Mahmood Hussain.

### Past Research Support

“Molecular mechanisms of chylomicron assembly” The aims are to study the secretion of free and esterified cholesterol by enterocytes. Agency NIH/NIDDK, RO1 DK46900. This grant started in Jan 1995 and had been renewed several times. The last funding period was from 8-1-2007 to 7-31-2013.

### Pending

None

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Girnun, Geoffrey D.</b>	POSITION TITLE <b>Associate Professor</b>		
eRA COMMONS USER NAME GEOFFREY_GIRNUN			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, medical, dental, veterinary, and business training, if applicable)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Iowa, Iowa City, IA	BS	1994	Physiology/Exer. Science
University of Iowa, Iowa City, IA	PhD	1999	Free Radical Radiation Bio

**A. Personal Statement**

Research in my lab is focused on linking fundamental aspects of metabolism and cancer. My research has focused on metabolic regulators and their role in disease. Currently my lab is focused on metabolic alterations in cancer that are driven by specific oncogenic changes. We are also focused on metabolic links underscoring the increase in colon cancer and GI cancer risk in obese and diabetic patients. In particular, we are also interested in how these metabolic changes can be used as biomarkers and in identifying cancer disparities in minority populations. We focus on metabolic regulators driving cancer by promoting metabolic changes associated with cancer as well as specific oncogenes and tumor suppressor genes and the metabolic pathways they control as a means of driving cancer. In addition, we study how metabolic pathways can drive signaling pathways that promote cancer.

**B. Positions and Honors.****Positions and Employment**

1994-1999	Ph.D. Student, Department of Free Radical and Radiation Biology, University of Iowa College of Medicine
1999-2003	Post-doctoral Fellow, Cell/Cancer Biology, Harvard Medical School and Dana-Farber Cancer Institute
2003-2007	Instructor in Cell/Cancer Biology, Harvard Medical School and Dana-Farber Cancer Inst.
2007-2013	Assistant Professor of Biochemistry and Molecular Biology, University of Maryland School of Medicine
2013-present	Associate Professor of Pathology, Stony Brook University School of Medicine
2013-present	Director, Program in Cancer Metabolism, Stony Brook Cancer Center

**Honors and Awards**

2006-2007	Madeline Franchi Ovarian Cancer Fund Award
2005-2007	Claudia Adams Barr Foundation Award (Co-PI)
2003-2008	NIH K01 Award
2001-2003	Individual National Research Service Award, NIDDK
2000-2001	National Research Service Award Trainee, NCI
1998-1999	Carver Medical Research Trust Award, University of Iowa College of Medicine.
1996	Radiation Research Society "Young Investigator" Award. The 44th Annual Radiation Research Society Meeting, Chicago, IL
1994-1998	Scotia Pharmaceuticals Ltd. (UK) Predoctoral Fellowship

**PUBLICATIONS:**

*Selected peer-reviewed publications (in chronological order):*

**Most relevant to the current application (From list of 26)**

1. Preuss, M., Girnun, G.D., Darby, C., Khoo, N., and Spector, A.A., Robbins, M.E.C. Role of antioxidant enzyme expression in the selective cytotoxic response of glioma cells to  $\gamma$ -linolenic acid supplementation. **Free Rad. Bio. Med.** 28:1143-1156, 2000. PMID: 10832077.
2. Girnun, G.D., Domann, F.E., Moore, S.A., Robbins, M.E. Identification of a functional peroxisome proliferator-activated receptor response element in the rat catalase promoter. **Mol. Endocrinol.** 16:2793-801, 2002. PMID: 12456800.
3. Girnun, G.D., Smith, W.M., Drori, S., Sarraf, P., Mueller, E., Eng, C., Nambiar, P., Rosenberg, D.W., Bronson, R.T., Edelmann, W., Kucherlapati, R., Gonzalez, F.J., Spiegelman, B.M. APC-dependent suppression of colon carcinogenesis by PPAR $\gamma$ . **Proc Natl Acad Sci USA.** 99:13771-6, 2002. PMCID: PMC129773.
4. Nambiar, P.R., Girnun, G.D., Lillo, N.A., Guda, K., Whiteley, H.E., Rosenberg, D.W. Preliminary analysis of azoxymethane induced colon tumors in inbred mice commonly used as transgenic/knockout progenitors. **Int. J. Oncol.** 22:145-50, 2003. PMID: 12469197.
5. \*Drori, S., \*Girnun, G.D., Mueller, E., Sarraf, P., Tou, L., Szwaja, J. Shivdasani, R., Spiegelman, B.M. Hic-5 regulates an epithelial program mediated by PPAR $\gamma$ . **Genes Dev.** 19:362-375, 2005. \*equal authorship PMCID: PMC546514.
6. Girnun, G.D., Naseri, E., Vafai, S., Qu, L., Szwaja, J., Bronson, R., Alberta, J., Spiegelman, B.M. Synergy between PPAR $\gamma$  ligands and platinum-based drugs in cancer. **Cancer Cell.** 11:395-406, 2007. PMCID: PMC2564847.
7. \*Girnun, G.D. Chen, L., Silvaggi, J., Drapkin, R., Chirieac, L.R., Padera, R.F., Upadhyay, R., Vafai, S.B., Wiessler, R., Mahmood, U., Naseri, E., Buckley, S., Li, D., Force, J., McNamara, K., Demetri, G., Spiegelman, B.M., \*Wong, K.K. Regression of drug-resistant lung cancer by the combination of rosiglitazone and carboplatin. **Clin. Cancer Res.** 14:6478-6486, 2008. PMCID: PMC2696122. \*Co-corresponding author
8. Girnun, G.D. PPAR $\gamma$ : A new independent marker for colorectal survival. **Gastroenterology.** 136:1157-1160, 2009. PMID: 19236969.
9. Souza, D.R., Pierce, A., Girnun, G., Passaniti, A. Glucose metabolism, transcriptional regulation and angiogenesis. 2009 **Current Topics Biochem. Res.** 11, 41-55.
10. Bhalla, K., Hwang, B.J., Dewi, R., Twaddell, W., Girnun, G.D. The metabolic coactivator PGC1 $\alpha$  promotes tumor growth by coordinating a gene expression program driving de novo fatty acid synthesis. **Cancer Res.** 71:6888-6898, 2011, PMID21914785
11. Bhalla, K, Hwang, B., Dewi, R., Choi, J-H., Dewi, R., Ou, L., Twaddell, W., Mclenithan, J., Voronkov, M., Stock, M., Perez, E., Stock, J., Pozharskiy, E., Girnun, G.D. N-Acetyl Farnesyl Cysteine is a novel class of PPAR $\gamma$  ligand with partial and full agonist activity *in vitro and in vivo*. **J. Biol Chem.** 286: 41626-41635, 2011 PMID: 21979952
12. Bhalla, K, Hwang, B., Dewi, R., Twaddell, W., Girnun, G.D. Metformin prevents hepatocellular carcinoma by antagonizing hepatic lipogenesis. **Cancer Prev Res.** 5: 544-552, 2012, PMID:22467080
13. Girnun, G.D. The diverse role of the PPAR $\gamma$  Coactivator-1 family of transcriptional coactivators. **Seminars in Cell and Developmental Biology. Cancer Cell Metabolism Issue.** 23:381-384, 2012, PMID: 22285815
14. Mehrabian, Z, Clerc, P, Carey, G, Michael Wei, M., Hwang, H., Girnun, G.D., Chen, H., Martin, S.S., Polster, B.M. Rapid detection of a "primed for death" state of BCL-2 dependence in cells using microplate-based respirometry. **PloS One**, 7:e42487, 2012, PMID:22880001
15. Vazquez, F., Lim, J.H., Chin, H., Girnun, G.D., Widlund, H.R., Spiegelman, B.M., Puigserver. The transcriptional coactivator PGC1 $\alpha$  defines a subset of human melanoma tumors with increased mitochondrial capacity and resistance to oxidative stress. **Cancer Cell**, 23:287-301, 2013.
16. Singh, A., Happel, C., Manna, S.K., Acquah-Mensah, G., Carratero, J., Kumar, S., Nasipuri, P., Krausz, K.W., Dewi, D, Boros, L.G., Gonzalez, F.J., Gabrielson, E., Wong, K.K., Girnun, G.D.\*, Biswal, S\*. Nrf2 regulates miR-1 and miR-206 to drive tumorigenesis. **J. Clin. Invest.** 123: 2921-2934, 2013. \*Co-corresponding author
17. Choe, C. Chumsri, S., Jones, L., Bhandary, L., Zhao, X.F., Lu, S., Goloubeva, O.G. Polster, B.M., Fiskum, G.M., Girnun, G.D. , Passaniti, A. Control of breast cancer metabolism and differentiation by the RUNX2 oncogene through modulation of SIRT6 suppressor gene expression. **Oncogene, Accepted pending revisions.**

18. Liu, WJ., Bhalla, K., Naseri, E., Hwang, B., Vafai, S., Anders, L., Sicinski, P., Girnun, G.D. Cyclin D1 suppresses gluconeogenesis via inhibition of PGC1alpha. **Diabetes**. 63:3266-78, 2014.

## D. Research Support

### Ongoing Research Support

1R01CA169919-01 Girnun, (PI) 07/09/2012-04/30/2017  
NIH/NCI \$211,248 3 cal

Title: Metabolic control of hepatocellular carcinoma by PGC1alpha

These studies are designed to determine the mechanisms by which PGC1alpha promotes liver cancer. In addition, they designed to determine whether PGC1 is a key mediator explaining increased liver cancer in diabetes.

1R01CA140492-01A1 (Co-I, S. Biswal-PI) 01/01/2010-12/31/2015  
NIH/NCI \$202,700 0.6 cal

Title: Regulation of tumorigenesis and therapeutic resistance by NRF2 in lung cancer. These studies are seeking to define the role of Nrf2 in lung cancer. Dr. Girnuns role is leading these studies in the aspects of metabolism and cancer. No overlap

VA Merit Award (Co-I, Passiniti-PI) 04/13/2013-03/31/2017  
Title: Transcriptional regulation of tumor growth \$263,000 0.6 cal

Start up funds (Girnun, PI)  
Office of the Vice president for Research and Cancer Center

### **Past support**

1R01CA169919-01 Girnun (PI) 09/01/2013-04/30/2014  
NIH/NCI- No cost extension 0.3 cal

Supplement- Collaborative Activities to Promote Metabolomics Research  
Metabolic control of hepatocellular carcinoma by PGC1alpha

KG081400 Girnun (PI) 08/01/08-07/31/2011  
Susan G. Komen Foundation Career Catalyst Development Award

Title: Bioenergetic Control of breast cancer growth by the transcriptional activator PGC1 $\alpha$ . The goal of this project is to determine the role of PGC1 $\alpha$  in breast cancer.

**BIOGRAPHICAL SKETCH**

NAME & CONTACT INFORMATION Michael A Frohman 438 CMM 631-632-1476		POSITION TITLE Professor and Chair of Pharmacology Director, Medical Scientist Training Program	
eRA COMMONS USER NAME & E-mail address mfrohman michael.frohman@stonybrook.edu			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
U. of Michigan; Ann Arbor	B.S. High Honors	1978	Chemistry & Cell & Molecular Biology
U. of Pennsylvania; Philadelphia	M.D., PhD.	1985	Medicine. Immunology
U. of Cal. at San Francisco	Postdoc	1986-92	Mammalian Developmental Biology

**A. Personal Statement:**

My laboratory cloned the mammalian family of lipid-signaling Phospholipase D genes (PLD1 in 1995, PLD2 in 1997, and MitoPLD in 2006) and has worked on them for the past 18 years while publishing nearly 100 peer-reviewed articles and reviews on PLD and other lipid signaling topics with additional ones in submission. PLD superfamily members are involved in many physiological and pathophysiological settings including immune defenses, cancer, neurodegenerative disease, diabetes, cardiovascular disease, and fertility. Among other approaches, we have recently been generating and publishing findings with mice lacking each of the PLD isoforms, and have uncovered a number of fascinating stories with human health relevance. Recent work has included exploring the potential of using a Phospholipase D small molecule inhibitor as a therapeutic in stroke, Alzheimer's Disease, cardiovascular disease and cancer progression settings.

I have been the Director of the Medical Scientist Training Program (MSTP, MD-PhD) at SBU for 13 years, renewing the T32 training grant three times. I am a graduate myself of an MSTP (U. Penn.), have been continuously funded by NIH for my research since the beginning of my faculty position in 1992, and have trained more than 50 students and fellows, approximately 20% of whom have been URM trainees. I have been an external reviewer of other Graduate and MD-PhD training programs since 2006 and have participated in study section reviews of MSTP T32 training grants and individual F-series NRSAs.

Many of the graduate student trainees in my lab have gone on to excellent research career paths, including URM ones:

Yeku Oladapo (Medgar Evers Coll.), 2006-2010; SBU MSTP (Pharmacology Graduate Program); U. Pitt. Int. Med.; Mt. Sinai Heme-Onc fellowship

Mary Osisami (SBU undergrad), 200—2012; Genetics Graduate Program (current: post-doc, University of Michigan)

Akua Bonsra (SBU undergrad), 2005 – 2010; Pharmacology Graduate Program; Regulatory Affairs Specialist at Technical Resources International, Inc

**B. Positions and Honors****Positions:**

1992-98; 98-03 Assistant & Associate Professor, Stony Brook University, Dept. Pharmacology  
 1995 – 2003 Director, Medical Pharmacology course, SBU School of Medicine  
 2002 - Director, Molecular Cloning Facility Core, Stony Brook University  
 2003 - Professor, Stony Brook University, Dept. Pharmacology  
 2003 - Director, Medical Scientist Training Program (MD/PhD, MSTP) at Stony Brook University  
 2007 - Chair, Department of Pharmacology

**Honors and Professional Activities:**

1977, 78 Michael Reese, U. Michigan Medical Student Summer Research Scholarship  
 1979-1985 Scholarship: NIH Medical Scientist Training Program

1984	Roy G. William Award
1986, 89	Post-doc Fellowships: American Cancer Society, Leukemia Society Senior Fellowship
1993	Basil O'Connor Young Investigator Award, March of Dimes
1994, 95, 96	NIH Cell Biology 1, HED-2 Study Section Special Reviewer
1998-2003	Editorial Board, Journal of Biological Chemistry
1998, 2000	Co-Chair, FASEB, ASPET Meetings on Phospholipases, PLD (Vermont, Boston)
1999 - 2003	NIH Special Emphasis Panel Study Section Ad-hoc Reviewer (ZRG1 SSS-Y 01)
2001	Chair, FASEB Meeting on Phospholipase D (Colorado)
2002, 2006, 2009	NIH P01 Special Emphasis Reviewer; NIH NRSA study section adhoc review panel
2004- 2007	Editorial Board, Journal of Endocrinology
2006-	External Advisory Board, Penn State Medical Scientist Training Program
2007-2008	Guest Co-Editor, Special issue on Phospholipase D in BBA Lipids
2007-	Editorial Boards, J. Functional Develop & Embryology; Molecular & Cellular Pharmacology
2009	NIH MPP Study Section Ad-hoc Reviewer
2010	External reviewer, Molecular Medicine Graduate Program, Med. Coll. Of Georgia
2010	Platform speaker, GPCR 2010 symposium, Helsinki, Finland
2011	Keynote speaker, National conference for MD-PhD training, Gwangju, South Korea
2012 -	Review Editorial Board of Frontiers in Mitochondrial Research
2012	NIH T32 Study Section Ad-hoc Reviewer for MSTP applications (February and June)
2013 -	Councilor, <i>Association of Medical School Pharmacology Chairs (AMSPC)</i>
2014 -	Editorial Board, " <i>Handbook of Experimental Pharmacology</i> "
2014 -	Advisory board, DO/PhD program, New York Institute of Technology

### C. Selected Peer-reviewed Publications (Selected from 184 total publications); h-index 61

#### Most relevant to the current application

- Choi, S.-Y., Huang, P., Chan, D.C., and Frohman, M.A. (2006) A common signaling lipid requirement for Mfn-mediated mitochondrial fusion and SNARE-regulated exocytosis. ***Nature Cell Biology*** 8:1255-62.
- Zhao, C., Du, G., Skowronek, K., Frohman, M.A., and Bar-Sagi, D. (2007) Phospholipase D2-generated PA couples EGFR stimulation to Ras activation by Sos. ***Nature Cell Biology***, 9:707-12. PMID: 17486115
- Yang, J.-S. et al. (2008) COPI vesicle fission: a role for phosphatidic acid and insight into Golgi maintenance. ***Nature Cell Biology***, 10:1146-53. PMID: 18776900
- Su, W., Yeku, O., Olepu, S., **Genna, A.**, Park, J.-S., Ren, H., Du, G., Gelb, M.H., Morris, A.J., and Frohman, M.A. (2009) FIPI, a PLD pharmacological inhibitor that alters cell spreading and inhibits chemotaxis. ***Molecular Pharmacology*** 75:437-46. PMID: 19064628
- Nishikimi et al. (2009) Sequential Regulation of DOCK2 Dynamics by Two Phospholipids during Neutrophil Chemotaxis. ***Science***, 324:384-7. PMID: 19325080
- Tsukahara et al. (2010) The novel second messenger Cyclic Phosphatidic Acid Negatively Regulates the Nuclear Hormone Receptor PPAR $\gamma$ . ***Molecular Cell***, 39:421-32.
- Elvers, M., Stegner, D., Hagedorn, I., Kleinschnitz, C., Braun, A., Kuijpers, M.E.J., Boesl, M., Chen, Q., Heemskerk, J.W.M., Stoll, G., Frohman, M.A., and Nieswandt, B. (2010) Impaired integrin  $\alpha$ IIb $\beta$ 3 activation and shear-dependent thrombus formation in mice lacking phospholipase D1. ***Science Signaling***, 3:1-10.
- Dall'Armi, C et al. (2010) The Phospholipase D1 Pathway Modulates Macroautophagy. ***Nature Communications***, 1:142-152.
- Huang, H., Gao, Q., Peng, X.X., Choi, S.-Y., **Sarma, K.**, Ren, H., Morris, A.J., and Frohman, M.A. (2011) piRNA-associated germline nuage formation and spermatogenesis require MitoPLD pro-fusogenic mitochondrial-surface lipid signaling. ***Developmental Cell***, 20:376-387.
- Huang, P., Yeku, O., Zong, H., Tsang, P., Su, W., Xu, X., Teng, S., Osisami, M., Kanaho, Y., Pessin, J.E., and Frohman, M.A. (2011) Phosphatidylinositol-4-Phosphate-5-Kinase  $\square$  Deficiency Alters Dynamics of Glucose-Stimulated Insulin Release to Improve Glucohomeostasis and Decrease Obesity in Mice. ***Diabetes***, 60:454-63.

Chen, Q., Hongu, T., Sato, T., Zhang, Y., Ali, W., Cavallo, J.-A., van der Velden, A., Tian, H., Di Paolo, G., Nieswandt, B., Kanaho, Y., and Frohman, M.A. (2012) Key roles for the lipid signaling enzyme PLD1 in the tumor microenvironment during tumor angiogenesis and metastasis. **Science Signaling**, 5:ra79.

- with accompanying Podcast in *Science Signaling*; highlighted in **Nature Cancer Reviews** (2013) and in the *Cancer Discovery Research Watch* by the American Assoc. for Cancer Research (Nov. 15<sup>th</sup>, 2012).

Osisami, M., Ali, W. and Frohman, M.A. A role for Phospholipase D3 in myotube formation. (2012). **PLoS One**, 7(3): e33341.

Stegner, D., Thielmann, I., Kraft, P., Frohman, M.A., Stoll, G., and Nieswandt, B. (2013) Pharmacological inhibition of phospholipase D protects mice from occlusive thrombus formation and ischemic stroke. **Arteriosclerosis, Thrombosis, and Vascular Biology**, 33:2212-7.

Li, S. et al.. (2013) High throughput sequencing analysis of natural regulatory and conventional T cell receptor repertoires during human H1N1 challenge. **Nature Communications**, 4:2333.

Akiyama, M., Hasegawa, H., Hongu, T., Frohman, M.A., Harada, A., Sakagami, H., and Kanaho, Y. (2014) Trans-regulation of oligodendrocyte myelination by neurons through small GTPase Arf6-regulated secretion of fibroblast growth factor-2. **Nature Communications**, 5:4744.

Mallipattu SK, Horne SJ, D'Agati V, Narla G, Liu R, Frohman MA, Dickman K, Chen EY, Ma'ayan A, Bialkowska AB, Ghaleb AM, Nandan MO, Jain MK, Daehn I, Chuang PY, Yang VW, He JC. (2015) Krüppel-like factor 6 regulates mitochondrial function in the kidney. **J. Clinical Investigation**, 125:1347-61.

#### D. RESEARCH SUPPORT

<b>R01</b> (PI, Frohman)	9/2012 - 8/2016
NIH GM100109 MitoPLD and RNA processing on the mitochondrial surface	
<b>R01</b> (PI, Frohman)	9/1/09 - 8/31/18
NIH GM084251	
Lipid-signaling pathways regulating mitochondrial morphology, energetics, and movement	
<b>Carol Baldwin Breast Cancer Award</b>	7/2013 – 6/2015
Inhibition of PLD1 as a therapeutic approach in breast cancer	

#### Mentored funding

NIH <b>NRSA</b> F31 Predoctoral fellowship to Rochelle Nelson	6/1/13 – 5/31/16
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Program Director/Principal Investigator (Last, First, Middle):

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Jian Cao	POSITION TITLE		
eRA COMMONS USER NAME (credential, e.g., agency login)	Professor of Medicine		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
School of Medicine, Zhengzhou University, Henan, China	M.D.	07/85	Medicine
Hospital Attached to Zhengzhou University, Henan, China	Intern	07/86	Medicine
Peking Union Medical College, Tsinghua University, Beijing, China	M.S.	07/92	Experimental Pathology
Cancer Institute, Kanazawa University, Kanazawa, Japan	Postdoctoral	05/95	Molecular Biology of Cancer
Stony Brook University, Stony Brook, NY	Postdoctoral	05/98	Cellular Biology of Cancer

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

**A. Personal Statement**

Dr. Cao is a Medical Scientist whose career began shortly after receiving his medical doctoral degree at Zhengzhou University School of Medicine (Henan Medical University), China. His interest in cancer research began during his training in experimental pathology in Peking Union Medical College, Tsinghua University (Chinese Academy of Medical Sciences) in Beijing, China, where he received his Master Degree of Sciences. Dr. Cao's research background was further strengthened in the field of molecular and cellular biology of cancer during his postdoctoral training in the laboratories of Dr. M. Seiki in Japan and Dr. S. Zucker in New York. He was among the first scientists to discover the membrane type 1-matrix metalloproteinase (MT1-MMP) and Cell Migration-inducing Protein (CEMIP) and demonstrated that these cancer metastasis-driving genes are targetable molecules aimed at preventing cancer dissemination. Dr. Cao joined the faculty at Stony Brook University in 1998 as an Assistant Professor, was promoted to Associate Professor in 2008 and then full Professor in 2014. His work at Stony Brook University led to: 1) the demonstration of the role of MT1-MMP in early cancer dissemination; 2) the discovery of an alternative approach targeting specific MMPs; 3) the identification of a novel surrogate marker in cancer cell migration/invasion; and 4) the development of a powerful screening tool for anti-cancer drug discovery using a three-dimensional cell culture system. His current research interests involve studying three broad aspects of cancer metastasis: 1) to better understand the mechanism of cancer invasion and metastasis; 2) to develop novel tools for early cancer diagnosis and prognosis; and 3) to identify inhibitors of cancer dissemination. Dr. Cao's long-term goal is to develop drugs to prevent metastasis.

**B. Positions and Honors****Positions and Employment**

1986-1989	Lecturer in Pathology, School of Medicine, Henan University, Henan, China
1998-2009	Assistant Professor of Medicine, Stony Brook University, Stony Brook, NY
2005-present	Member, Institute of Chemical Biology & Drug Discovery (ICB&DD)/Stony Brook University
2008-present	Member, Molecular & Cellular Biology Graduate Program/Stony Brook University
2008-present	Member, Molecular & Cellular Pharmacology Graduate Program/Stony Brook University
2008-present	Member, Molecular Genetics Graduate Program/Stony Brook University
2008-present	Assistant Professor of Pathology, Stony Brook University, Stony Brook, NY
2009-2014	Associate Professor of Medicine, Stony Brook University, Stony Brook, NY
2011-present	Member, Chemical Biology Training Program/Stony Brook University
2014-present	Professor of Medicine, Stony Brook University, Stony Brook, NY

Program Director/Principal Investigator (Last, First, Middle):

**Other Experience and Professional Memberships**

1996-present	Member, American Association for Cancer Research (AACR)
2005-2006	Komen Breast Cancer Foundation, Tumor Biology and Cell Biology
2006-2007	Komen Breast Cancer Foundation, Postdoctoral Fellowship Committee
2006	The Israel Science Foundation (Ad hoc)
2008-2009	DOD Breast Cancer Research Program (BCRP) IDEA and Synergistic IDEA Awards
2009-2010	DOD Breast Cancer Research Program (BCRP) Concept Award/Pathobiology-1
2010-2011	DOD Breast Cancer Research Program (BCRP) Concept Award/Pathobiology-3
2010	National Science Foundation (NSF), Chemistry of Life Processes (CLP) Program
2011	DOD Breast Cancer Research Program (BCRP) Postdoctoral Fellowship Award
2012	DOD Prostate Cancer Research Program (PCRP) Idea Development Award, Pathobiology-2
2012	DOD Prostate Cancer Research Program (PCRP) Idea Development Award, Pathobiology-1(Ad hoc)
2012	DMP Study Section, NIH
2012	VA Oncology Merit Review Panel
2013	DMP Study Section, NIH
2013	Breast Cancer Training-PBY peer review panel
2013	The Israel Science Foundation (Ad hoc)
2013	Carol M. Baldwin Breast Cancer Foundation
2012	VA Oncology Merit Review Panel
2013	DOD Prostate Cancer Research Program (PCRP)-Cell Biology-1
2013	2014 State University of New York Collaboration Fund Panel-3 Chemistry
2014	DOD Breast Cancer Training-PBY peer review panel
2014	NIH Director's Early Independence Award peer review panel
2014	DOD Breast Cancer Research Program_ Breakthrough Award peer review panel
2014	DMP Study Section, NIH
2014	VA Oncology Merit Review Panel
2015	DOD Breast Cancer Research Program_ Breakthrough Award peer review panel
2012-present	Academic Editor: PLoS ONE, The Public Library of Science
2012-present	Member, Editorial Board: Journal of Cancer Research & Therapy, NobleResearch Publisher
2012-present	Managing Editor, Frontiers in Bioscience
2012-present	Member, Editorial Board: Dataset Papers in Biology, Hindawi Publishing Corporation
2012-present	Member, Editorial Board: International Journal of Chronic Diseases, Hindawi Publishing Corporation
2013-present	Member, Editorial Advisory Board, Current Cancer Drug Targets, Bentham Science Publishers
2006-2008	Member, Subcommittee on Animal Studies (IACUC) of VA Hospital, Northport, NY
2008-present	Serve as an interviewer for recruiting graduate students for MCB, Genetics, Pharmacology, and Medical Scientist Training Program (M.D./Ph.D.), Stony Brook University
2008-present	Member/co-chair, The Admissions Committee for the Molecular and Cell Biology and Genetics Programs/Stony Brook University
2009-2010	Member of Undergraduate Council of the University Senate, Stony Brook University
2012-present	Executive Core Oversight Committee, School of Medicine, Stony Brook University
2012-2015	Central Microscopy Imaging Center Core Advisory Committee, School of Medicine, Stony Brook University
2012-present	Member of Graduate and Research Committee, University Faculty Senate of the State University of New York (SUNY System)
2012-present	Member of the Department of Medicine's Research Committee, Stony Brook University

**Honors:**

1982-1986	Scholarship to School of Medicine, Zhengzhou University, Henan, China
1982-1986	Distinguished Graduate Student Award, School of Medicine, Zhengzhou University, Henan, China
1993-1994	Research Fellowship award, Ministry of Education, Science, and Culture of Japan
1997-1998	Research Fellowship award, American Heart Association
1998	AACR-Bristol-Myers Squibb Young Investigator Award, New Orleans, LA

Program Director/Principal Investigator (Last, First, Middle):

1998-2001 Postdoctoral Traineeship award, US Army Medical Research and Materiel Command  
 2001 American Association for Cancer Research Scholar-in-Training Award, New Orleans, LA  
 2001 Gordon Research Conference-Matrix Metalloproteinases travel award, Italy  
 2001-2004 Scientist Development Grant award, the American Heart Association  
 2001-2004 New Investigator Award by US Army Medical Research and Materiel Command (PCRP01)  
 2002 American Association for Cancer Research, Scholars in Cancer Research, San Francisco, CA  
 2014 Basic Science Award, Dept. Of Medicine, Stony Brook University

**C. Selected Peer-reviewed Publications (Selected from 55 peer-reviewed publications)**Most relevant to the current application

1. **Cao J**, Kozarekar P, Pavlake M, Chiarelli C, Bahou WF, Zucker S. (2004). Distinct roles for the catalytic and hemopexin domains of membrane type 1-matrix metalloproteinase metalloproteinase in substrate degradation and cell migration. **J Biol Chem**. 279(14):14129-39. PMID: 14729674
2. **J. Cao**, M. Hymowitz, C. Conner, W. Bahou and S. Zucker (2000). The propeptide domain of membrane type 1-matrix metalloproteinase acts as an intramolecular chaperon when expressed in trans with the mature sequence in COS-1 cells. **J.Biol.Chem.**, Vol.275:29648-29653, PMID:10889191
3. **Cao J**, Chiarelli C, Kozarekar P, and Adler HL. (2005). MT1-MMP Promotes Human Prostate Cancer Invasion and Metastasis. **Thromb Haemost**. 93:770-8, PMID: 15841326
4. **Cao J**, Rehemtulla A, Pavlaki M, Kozarekar P, Chiarelli C. (2005). Furin directly cleaves proMMP-2 in the trans-Golgi network resulting in a non-functioning proteinase. **J Biol Chem**. 280:10974-80. PMID: 15637056
5. **Cao J**, Chiarelli C, Richman O, Zarrabi K, Kozarekar P, Zucker S. (2008). MT1-MMP induces epithelial-to-mesenchymal transition (EMT) in prostate cancer. **J Biol Chem**. 283(10):6232-40. PMID: 18174174
6. Antoine Dufour, Nicole Sampson, Stanley Zucker and **Jian Cao** (2008). Role of the Hemopexin Domain of Matrix Metalloproteinases in Cell Migration, **J Cell Physiol**. 217(3):643-51. PMID: 18636552
7. Dufour A, Zucker S, Sampson NS, Kuscus C, **Cao J**. (2010). Role of matrix metalloproteinase-9 (MMP-9) dimers in cell migration: design of inhibitory peptides\* **J. Biol. Chem.**, 12;285(46):35944-56. PMID: 20837483 \* This work was featured in F1000Prime, Post-publication Peer Review, Jan. 2011
8. Antoine Dufour, Nicole S. Sampson, Jian Li, Cem Kuscus, Robert Rizzo, Jennifer L. DeLeon, Jizu Zhi, Nadia Jaber, Eric Liu, Stanley Zucker and **Jian Cao** (2011). Small Molecule Anti-Cancer Compounds Selectively Target the Hemopexin Domain of Matrix Metalloproteinase-9 (MMP-9)\*, **Cancer Res**. 71(14):4977-88. PMID:21646471  
 \* This work was featured in **SciBX** (JUNE 23, 2011 • VOLUME 4 / NUMBER 25), a publishing collaboration between **BioCentury** Publications, Inc. and **Nature** Publishing Group.
9. Kevin Zarrabi, Antoine Dufour, Jian Li, Cem Kuscus, Jizu Zhi, Youjun Hu, Nicole S. Sampson, Stanley Zucker, and **Jian Cao** (2011). Inhibition of matrix metalloproteinase-14 (MMP-14)-mediated cancer cell migration\* **J. Biol. Chem**. 286(38):33167-77. PMID:21795678  
 \* This work was featured in F1000Prime, Post-publication Peer Review, Aug. 2011
10. Nguyen HL, Zucker S, Zarrabi K, Kadam P, Schmidt C, **Cao J** (2011). Oxidative stress and prostate cancer progression are elicited by membrane-type 1 matrix metalloproteinase. **Mol Cancer Res**. 9(10):1305-18. PMID: 21849471
11. Li J, Zucker S, Pulkoski-Gross A, Kuscus C, Karaayvaz M, Ju J, Yao H, Song E, **Cao J**. (2012) Conversion of Stationary to Invasive Tumor Initiating Cells (TICs): Role of Hypoxia in Membrane Type 1-Matrix Metalloproteinase (MT1-MMP) Trafficking. **PLoS One** 7(6):e38403; PMID:22679501.  
 \* This work was featured in Faculty of 1000, Post-publication Peer Review, June 2012
12. Cem Kuscus, Nikki Evensen, Deborah Kim, You-Jun Hu, Stanley Zucker, and **Jian Cao** (2012):Transcriptional and Epigenetic Regulation of KIAA1199 Gene Expression In Human Breast Cancer \*. **PLoS One** 2012;7(9):e44661, PMID 22970280.  
 \* This work was featured in World Biomedical [ISSN: 2328-0166]
13. Nikki A Evensen, Cem Kuscus, Kevin Zarrabi, Antoine Dufour, Pournima Kadam, You-jun Hu, Ashleigh Pulkoski-Gross, Hoang-Lan Nguyen, Wadie F. Bahou, Stanley Zucker, and **Jian Cao** (2013) Unraveling the Role of KIAA1199, A Novel Endoplasmic Reticulum Protein in Cancer Cell Migration, **J Natl Cancer Inst**. 105(18):1402-16. PMID: 23990668
14. Nikki A. Evensen, Jian Li, Jie Yang, Xiaojun Yu, Nicole S. Sampson, Stanley Zucker, and **Jian Cao** (2013)

Program Director/Principal Investigator (Last, First, Middle):

Development of a High-Throughput Three-Dimensional Invasion Assay for Anti-Cancer Drug Discovery, **PLoS One** December 2013; 8 (12):e82811. PMID: 24349367

15. Pulkoski-Gross AE, Li J, Zheng C, Li Y, Ouyang N, Rigas B, Zucker S, **Cao J** Repurposing the Anti-psychotic Trifluoperazine as an Anti-metastasis Agent. **Mol Pharmacol**. 2014 Dec 31. PMID: 25552486 [Epub ahead of print]

#### D. Research Support

##### Ongoing Research Support

1R01CA166936-01 (NIH/NCI) Cao (PI) 04/02/2012- 03/30/2017

Title: Integrating Anti-invasive and Anti-growth Therapies Targeting Cancer Metastasis

The major goals of this proposal are to understand the interplay between tumor initiating cells (TICs) and their microenvironment during the transition to invasion and metastasis, as well as to develop a novel treatment reagent to specifically induce invasive TIC death in a preclinical setting.

##### Completed Research Projects for the Past Three Years

\* Carol M. Baldwin Breast Cancer Research Award Cao (PI) 08/01/12-07/31/14

Title: A Novel 3-Dimensional High-Throughput Assay for Targeting Invasive Breast Cancer Cells

The goal of this proposal is to develop a phenotypic screening assay that monitors breast cancer cell invasion in a 3-D environment.

\* R01 CA113553-05 (NCI/NIH) Cao (PI) 04/01/2006- 03/31/2012

Title: Targeting the PEX Domain of MT1-MMP: Novel Cancer Therapy

The major goals of this proposal are to examine the role of MT1-MMP in early stage of cancer invasion and develop specific inhibitors against the hemopexin (PEX) domain of MT1-MMP.

\* R01 CA113553-04S1 (NCI/NIH), Cao (PI, Mentor) 08/01/07- 03/31/11

Title: Targeting the PEX Domain of MT1-MMP: Novel Cancer Therapy This supplemental grant supports Dr. Nguyen's Postdoctoral Traineeship under the PI's R01 grant.

\* Centocor, Inc. Collaborative Award Cao (PI) 09/01/05–12/31/10

The purpose of this award is to improve academic-industry collaboration for evaluation the effect of Centocor's Extracellular Matrix Metalloproteinase Inducer (EMMPRIN) antibody on an orthotopic breast cancer animal model.

\* DOD BCRP Concept Award (W81XWH1010415) Cao (PI) 09/01/10 - 10/31/12

Title: Development of a Novel Cell-Based, High-Throughput Screening Assay for Anti- metastatic Breast Cancer Stem Cell Drug Discovery

The primary goal of this pilot study is to develop a novel cell-based high throughput screening (HTS) assay which allows for the simultaneous determination of metastatic breast cancer stem cell (CSC) migratory ability as well as proteolytic activity.

\* DOD BCRP Concept Award (W81XWH0910358) Shi and Cao (PIs) 09/01/09 - 10/31/11

Title: Detection of Circulating Cancer Cells Using Nano Acoustic Waves

The aim of this proposal is to detect circulating tumor cells (CTCs) in blood of patients with breast cancer using nano acoustic wave (NAW) technology. This is a joint effort between Stony Brook University and Stevens Institute of Technology (NJ).

\* Carol M. Baldwin Breast Cancer Research Award Cao (PI) 11/01/09-10/31/11

Title: Targeting Metastatic Breast Cancer Stem Cell Invasion

The goal of this application is to identify specific inhibitory hits targeting breast cancer stem cells with invasive properties by screening the compound libraries using our 3D invasion HTS assay.

\* Organomed Corporation. Collaborative Award Cao (PI) 06/18/10–12/31/11

Title: Evaluation of Novel Synthetic Compounds Targeting Cancer Cell Proliferation

The purpose of this award is to improve academic-industry collaboration for evaluation the effect of newly generated synthetic compounds inducing cancer cell apoptosis. The compounds are being examined using in vitro and in vivo cancer models.

\* Stony Brook University-Brookhaven National Lab Seed Grant Cao, Sampson, and Fowler (PIs) 09/01/10-08/31/11

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Scharer, Orlando D.</b>		POSITION TITLE Professor of Pharmacological Sciences and Chemistry	
eRA COMMONS USER NAME (credential, e.g., agency login) OSHARER			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
ETH, Zürich, Switzerland	Diplom	1991	Chemistry
Harvard University, Cambridge, MA	PhD	1996	Chemistry
Erasmus University, Rotterdam, Netherlands	Postdoc	1996-99	Genetics/Biochemistry

**A. PERSONAL STATEMENT**

Research in my laboratory combines organic chemistry, biochemistry and molecular and cellular biology to study the mechanism of mammalian nucleotide excision repair (NER) and interstrand crosslink (ICL) repair. We are interested in two fundamental questions: 1) What are the molecular mechanisms by which DNA repair pathways counteract carcinogenesis and 2) How might we exploit our understanding of DNA repair pathways to improve cancer chemotherapy. Our laboratory has extensive experience in the synthesis of site-specific DNA adducts, including interstrand crosslinks (ICLs) formed by cisplatin, nitrogen mustards and chloro ethyl nitroso ureas as well as adducts formed by environmental mutagens such as AAF. We have used such substrates extensively for the study of the NER and ICL repair pathways. Our studies of the NER pathway have yielded a new model of how the activity of the two endonucleases ERCC1-XPF and XPG are regulated and coordinated to ensure smooth progression through the NER pathway. Our studies of ERCC1-XPF have furthermore provided a molecular bases for how mutations in this heterodimer can lead to three genetic disorders: xeroderma pigmentosum, Fanconi anemia and the progeria XFE syndrome. Our studies using our synthetic ICLs have shown how these lesions interact with translesion synthesis polymerases and yielded important insights into the mechanisms of replication-dependent and -independent ICLs. To date I have trained 18 graduate students and 4 postdocs and numerous undergraduates and rotation students in my laboratory.

**B. POSITION AND HONORS****Positions and Employment**

1999-2005 Group Leader, START Fellow at the Institute of Molecular Cancer Research, University of Zürich, Switzerland.  
2002-2005 Lecturer, Department of Chemistry, ETH Zurich, Switzerland  
2005-2011 Associate Professor (with tenure) of Pharmacological Sciences and Chemistry, Stony Brook University, NY  
2005- Member, Institute of Chemical Biology and Drug Discovery, Stony Brook University, NY  
2005- Member, Molecular and Cellular Biology and Biochemistry and Biophysics Graduate Programs, Stony Brook University, NY  
2011- Professor of Pharmacological Sciences and Chemistry, Stony Brook University, NY

**Awards**

1996-1997 Post doctoral fellow of the Swiss National Science Foundation  
1997-1999 Human Frontier Science Program long-term postdoctoral fellow  
1997 Awarded EMBO postdoctoral fellowship  
1999-2005 START fellow of the Swiss National Science Foundation  
2001 EMBO Young Investigator Award  
2005 NYSTAR Faculty Development Award

**Selected Professional activities**

2015	Chair, Mammalian DNA Repair Gordon Research Conference
2013	Vice Chair, Mammalian DNA Repair Gordon Research Conference
2013-	Contributing member; <i>Faculty of 1000</i>
2012-	Editorial Board, Environ Mol Mutagen
2011	Guest Editor for special issue of DNA Repair on Nucleotide Excision Repair
2014	NIH CE study section, chair
2012-2013	NIH CE study section, co-chair
2009-2014	NIH CE study section, regular member
2008-2009	NIH CE study section, Ad hoc member
2008	NCI Molecular Oncology P01 SEP member
2001-	External Reviewer for NSF, HFSP, ERC, EMBO, AICR, Cancer Research UK, Wellcome Trust, Research Fondation, Research Cooperation, A*STAR, Swiss Cancer League
2000-	Ad hoc reviewer for >40 Journals, including Science, Nature, Nat Cell Biol, Nat Struct Mol Biol, Nat Chem Biol, Cell, Mol Cell, Genes Dev, EMBO J, PNAS, PLoS Biology, MCB, Angew Chem, JOC, Org Lett.

**C. SELECT RECENT PEER-REVIEWED PUBLICATIONS** (from a total of 71, h-index = 32)

1. Mukherjee S, Guainazzi A, **Schärer OD** (2014) Synthesis of structurally diverse DNA interstrand crosslinks using postsynthetic reductive amination. **Nucleic Acids Res**, 42, 7429-7435 PMCID: PMC4066762.
2. Hodskinson MR, Silhan J, Crossan GP, Garaycochea JI, Mukherjee S, **Schärer OD**, Patel KJ (2014) Mouse Slx4 is a tumour suppressor that stimulates the activity of the nuclease Xpf-Ercc1 in DNA crosslink repair. **Mol Cell**, 54, 472-484. PMCID: PMC4017094.
3. Guillemette S, Branagan A, Peng M, Dhruva A, **Schärer OD**, Cantor SB (2014) FANCD1 localization by mismatch repair is vital to maintain genomic integrity after UV irradiation. **Cancer Res**, 74, 932-944. PMCID: in progress.
4. Bogliolo M, Schuster B, Stoepker C, Derkunt B, Su Y, Raams A, Trujillo JP, Minguillón J, Ramírez MJ, Pujol R, Casado JA, Baños R, Rio P, Knies K, Zúñiga S, Benítez J, Bueren JA, Jaspers NGJ, **Schärer OD**, Winter JP, Schindler D, Surrallés J (2013) Mutations in ERCC4, encoding the DNA-repair endonuclease XPF, cause Fanconi anemia. **Am J Hum Genet**, 92, 800-806. PMCID: PMC3644630.
5. Su Y, Orelli B, Madireddy A, Niedernhofer LJ, **Schärer OD** (2012) Multiple domains of ERCC1-XPF contribute to DNA binding in nucleotide excision repair **J Biol Chem**, 287, 21846-21855. PMCID: PMC3381147.
6. Enoiu M, Jiricny J, **Schärer OD** (2012) Repair of cisplatin-induced DNA interstrand crosslinks by a replication-independent pathway involving transcription-coupled repair and translesion polymerases. **Nucl Acids Res**, 40, 8593-8964. PMCID: PMC3467066.
7. Enoiu M, Ho TV, Long DT, Walter JC, **Schärer OD** (2012) Construction of plasmids containing site-specific DNA interstrand crosslinks for biochemical and cell biological studies. **Methods Mol Biol** 920, 203-219.
8. Yeo J-E, Khoo A, Fagbemi AF, **Schärer OD** (2012) The efficiencies of damage recognition and excision correlate with duplex destabilization induced by acetylaminofluorene adducts in human nucleotide excision repair. **Chem Res Tox**, 25, 2462-2468. PMCID: PMC3502718.
9. Hentschel S, Alzeer J, Angelov T, **Schärer OD**, Luedtke NW (2012) Synthesis of DNA interstrand crosslinks using a photocaged nucleobase. **Angew Chem**, 51, 3466-3469. Policy Exempt - Not resulting from NIH funding.
10. Fu YV, Yardimci H, Long DT, Ho TV, Guainazzi A, Bermudez VP, Hurwitz J, van Oijen A, **Schärer OD**, Walter JC (2011) Selective bypass of a lagging strand roadblock by the eukaryotic replicative DNA helicase. **Cell** 146, 931-941. PMCID: PMC3209622.
11. Ho TV, Guainazzi A, Derkunt SB, Enoiu M, **Schärer OD** (2011) Structure-dependent translesion synthesis of major groove DNA interstrand crosslinks. **Nucl Acids Res** 39, 7455-7464. PMCID: PMC3177197.

12. Guainazzi A, Campbell AJ, Angelov T, Simmerling C, **Schärer OD** (2010) Synthesis and molecular modeling of a nitrogen mustard DNA interstrand crosslink. **Chem Eur J** 16, 12100-12103.
13. Orelli B, McClendon BT, Tsodikov, OV, Ellenberger T, Niedernhofer LJ, **Schärer OD** (2010) The interaction between ERCC1 and XPA is required for nucleotide excision repair, but not other DNA repair pathways. **J Biol Chem** 285, 3705-3712.
14. Ahmad A, Enzlin JH, Wijgers N, Raams A, Appeldoorn E, Theil AE, Hoeijmakers JHJ, Vermeulen V, Jaspers NGJ, **Schärer OD\***, Niedernhofer LJ\* (2010) Aberrant sub-cellular localization of DNA repair protein XPF: the molecular basis for extracutaneous symptoms in xeroderma pigmentosum. **PLoS Genet** 6, e1000871. PMID:PMC2832669. \*Co-corresponding authors
15. Knipscheer P, Räsche M, Smorgorzewska A, Enoiu M, Ho TV, **Schärer OD**, Elledge SJ, Walter JC (2009) The Fanconi anemia pathway promotes replication-dependent DNA interstrand crosslink repair. **Science** 326, 1698-701. PMID: PMC2909596.

## D. RESEARCH SUPPORT

### Ongoing Research Support

R01CA165911-01      Schärer, OD (PI)      07/01/12-04/30/17

NIH/NCI

Synthesis, structure and repair of DNA interstrand crosslinks.

Role: PI

The major goals of this project are to synthesize and structurally characterize DNA interstrand crosslinks and to characterize how they are processed in cell extracts and by DNA polymerases.

3P01CA092584-11      Tainer, JA (PI)      09/01/11-08/31/16

NIH/NCI

Structural Cell Biology of DNA Repair Machines

Role: Senior Investigator

Structural and biochemical approaches to study the interaction of ERCC1-XPF with XPA, SLX4 and DNA

NN      Begley TJ; Schärer, OD (Co-PIs)      11/01/13-10/31/15

SUNY/RF Research Collaboration Fund (PIs: Begley & Schärer)

Diagnostic Tools for Assessing the Levels and Repair of Cisplatin DNA Adducts in Tumors

Role: Co-PI

Generate antibodies with specificity against various cisplatin-DNA adducts

1R13 CA192553      Schärer, OD (PI)      11/07/14-03/13/15

NIH/NCI/NIA/NIEHS

2015 Mammalian DNA Repair Gordon Research Conference & Gordon Research Seminar

Role: PI

Support for the organization of a Gordon Research Conference and Seminar

### Recently Completed Research Support

P01ES04068      Grollman, A (PI)      07/01/07-08/31/12

NIH/NIEHS

Molecular Toxicology of DNA adducts

Role: Co-Investigator

R01GM080454-01      Schärer, OD (PI)      09/24/07-08/31/11

NIH/NIGMS

Coordination of late steps in the human nucleotide excision repair

R01GM080454-S1      Schärer, OD (PI)      08/14/09-06/31/11

NIH/NIGMS

Coordination of late steps in the human nucleotide excision repair

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Kollmar, Richard	POSITION TITLE Associate Professor, Cell Biology; Assistant Professor and Director of Basic Research, Otolaryngology		
eRA COMMONS USER NAME (credential, e.g., agency login) RKOLLMAR			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Julius-Maximilians-Universität Würzburg, Germany	(Vordiplom)	1983-1985	Chemistry
Ludwigs-Maximilians-Universität München, Germany	Dipl. Chem.	1985-1988	Chemistry
University of Wisconsin–Madison	Ph. D.	1988-1993	Cell and Molecular Biology
University of Texas Southwestern Medical Center	Postdoc	1993-1995	Neuroscience
Rockefeller University	Postdoc	1995-2003	Neuroscience

### A. Personal Statement

I am well suited to join Dr. Martello-Rooney in developing zebrafish into an affordable and high-throughput system to characterize pancreas other GI-derived biopsies from the underserved patient population. First, I have a broad scientific background in several disciplines—graduate training in cell and molecular biology obtained in the McArdle Laboratory for Cancer Research at the University of Wisconsin and postdoctoral training in neuroscience at Southwestern Medical Center and Rockefeller University. Second, I have more than two decades of experience working with zebrafish, starting out with the Neurobiology Course at the Marine Biological Laboratory in Woods Hole, establishing and leading a genetic screen as a postdoc, and continuing to study the molecular genetics of otolith formation in my own laboratory to the present day. We have identified several novel otolith proteins by using proteomics and are investigating their function both in vivo and in vitro. Third, I am leading a scientific collaboration with colleagues in Otolaryngology and in Physiology & Pharmacology to test novel treatments to promote regeneration of the recurrent laryngeal nerve after injury in the rat. This translational project extends a previous collaboration on Wnt signaling and the regeneration of spiral ganglion neurons. Both the otolith and the nerve-regeneration studies have been supported by external funding. Finally, with joint appointments in Cell Biology and Otolaryngology and as the Director of Basic Research for Otolaryngology, I have extensive experience in mentoring research by graduate and medical students, postdoctoral fellows, and residents.

### B. Positions and Honors

#### Positions and Employment

1988-1993	Research Assistant (with Peggy Farnham), McArdle Laboratory for Cancer Research, University of Wisconsin
1993-1995	Research Associate (with A. James Hudspeth), Howard Hughes Medical Institute and Department of Cell Biology and Neuroscience, University of Texas Southwestern Medical Center at Dallas
1995-2003	Research Associate (with A. James Hudspeth), Howard Hughes Medical Institute and Laboratory of Sensory Neuroscience, Rockefeller University, New York
2003-2009	Assistant Professor, Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign
2004-2009	Affiliate, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign
2009-2011	Visiting Associate Professor, Department of Cell Biology, SUNY Downstate Medical Center
2011-present	Assistant Professor, Department of Otolaryngology, SUNY Downstate Medical Center

2011-present Director of Basic and Translational Research, Department of Otolaryngology, SUNY Downstate Medical Center  
 2012-present Associate Professor, Department of Cell Biology, SUNY Downstate Medical Center  
 2013-present Director, Molecular and Cellular Biology Program, School of Graduate Studies, SUNY Downstate Medical Center

#### Other Experiences and Professional Memberships

1993 Neurobiology Course, Marine Biological Laboratory, Woods Hole, MA  
 2002-present Member, Association for Research in Otolaryngology  
 2003-present Member, Society for Neuroscience  
 2013-2015 NIH Special Emphasis Panel/Scientific Review Group on Xenopus Genetics and Genomics  
 2013-present Member, American Academy for Otolaryngology-Head and Neck Surgery

#### **C. Selected Peer-reviewed Publications (Out of 18 total)**

1. **Kollmar R**, Montgomery LG, Fak J, Henry LJ, Hudspeth AJ. Predominance of the  $\alpha 1D$  subunit in L-type voltage-gated  $Ca^{2+}$  channels of hair cells in the chicken's cochlea. *Proc Natl Acad Sci U S A*. 1997 Dec 23;94(26):14883-8. [PMC25132]
2. **Kollmar R**, Fak J, Montgomery LG, Hudspeth AJ. Hair cell-specific splicing of mRNA for the  $\alpha 1D$  subunit of voltage-gated  $Ca^{2+}$  channels in the chicken's cochlea. *Proc Natl Acad Sci U S A*. 1997 Dec 23;94(26):14889-93. [PMC25133]
3. **Kollmar R**. Who does the hair cell's 'do? Rho GTPases and hair-bundle morphogenesis. *Curr Opin Neurobiol*. 1999 Aug;9(4):394-8. Review. [PMID10448167]
4. **Kollmar R**, Nakamura SK, Kappler JA, Hudspeth AJ. Expression and phylogeny of claudins in vertebrate primordia. *Proc Natl Acad Sci U S A*. 2001 Aug 28;98(18):10196-201. [PMC56938]
5. Starr CJ, Kappler JA, Chan DK, **Kollmar R**, Hudspeth AJ. Mutation of the zebrafish choroideremia gene encoding Rab escort protein 1 devastates hair cells. *Proc Natl Acad Sci U S A*. 2004 Feb 24;101(8):2572-7. [PMC356991]
6. Kappler JA, Starr CJ, Chan DK, **Kollmar R**, Hudspeth AJ. A nonsense mutation in the gene encoding a zebrafish myosin VI isoform causes defects in hair-cell mechanotransduction. *Proc Natl Acad Sci U S A*. 2004 Aug 31;101(35):13056-61. [PMC516516]
7. López-Schier H, Starr CJ, Kappler JA, **Kollmar R**, Hudspeth AJ. Directional cell migration establishes the axes of planar polarity in the posterior lateral-line organ of the zebrafish. *Dev Cell*. 2004 Sep;7(3):401-12. [PMID15363414]
8. Asai Y, Chan DK, Starr CJ, Kappler JA, **Kollmar R**, Hudspeth AJ. Mutation of the zebrafish atrophin2 gene disrupts signaling by fibroblast growth factor during development of the inner ear. *Proc Natl Acad Sci U S A*. 2006 Jun 13;103(24):9069-74. [PMC1474007]
9. Vieira M, Christensen BL, Wheeler BC, Feng AS, **Kollmar R**. Survival and stimulation of neurite outgrowth in a serum-free culture of spiral ganglion neurons from adult mice. *Hearing Res*. 230: 17-23, 2007. [PMID17521837; manuscript available at <http://hdl.handle.net/2142/1353>]
10. Kang YJ, Stevenson A, Yau P, **Kollmar R**. Sparc Protein Is Required for Normal Growth and Mineralization of Zebrafish Otoliths. *JARO—Journal of the Association for Research in Otolaryngology* 9: 436-451, 2008. [PMC2580808]
11. Shah SM, Kang YJ, Christensen BL, Feng AS, **Kollmar R**. Expression of Wnt receptors in adult spiral ganglion neurons: Frizzled 9 localization at growth cones of regenerating neurites. *Neuroscience* 164: 478-487, 2009. [PMC2761969; manuscript also available at <http://hdl.handle.net/2142/14823>]
12. Shah SM, Patel CH, Feng AS, **Kollmar R**. Lithium alters the morphology of neurites regenerating from cultured adult spiral ganglion neurons. *Hear Res*. 304: 137-44, 2013. [PMC3773701]
13. Mor N, Naggar I, Das O, Nakase K, Silverman JB, Sundaram K, Stewart M, **Kollmar R**. Quantitative video laryngoscopy to monitor recovery from recurrent-laryngeal-nerve injury in the rat. *Otolaryngol Head Neck Surg*. in press.

#### **D. Research Support**

##### Ongoing Research Support

1 R21 DC013629-01A1 (NIH/NIDCD)      Kollmar (PI)      12/1/14-11/30/16  
Restoration of Recurrent-Laryngeal-Nerve Function after Injury in a Rat Model  
This study aims to develop procedures for a reducible injury to the recurrent laryngeal nerve and to test the effect of systemic lithium administration on recovery from unilateral vocal-fold paralysis in rats.  
Role: Principal Investigator

Completed Research Support

2013 AAO-HNSF Percy Memorial Research Award      Kollmar (PI)      7/1/13-6/30/14  
Restoration of recurrent-laryngeal-nerve function after injury in a rat model  
This study aims to develop surgical and pharmacological methods to promote nerve regeneration in rats with unilateral vocal-fold paralysis.  
Role: Principal Investigator

1 R01 DC006962-01A1 (NIH/NIDCD)      Kollmar (PI)      7/1/05-6/30/13  
Molecular Genetics of Otolith Formation in the Zebrafish  
This study aims to identify the constituent proteins of otoliths and elucidate their role in otolith formation.  
Role: Principal Investigator

National Organization for Hearing Research      Kollmar (PI)      2/1/2008-1/31/2009  
Interaction of Wnt-Frizzled- and BDNF-signaling during neurite regeneration from adult spiral ganglion neurons  
The long-term goal of this translationally-oriented project is to improve the fidelity of sound perception with cochlear implants by stimulating the outgrowth of neurites from damaged spiral ganglion neurons.  
Role: Principal Investigator

## BIOGRAPHICAL SKETCH

NAME Shroyer, Kenneth Reed	POSITION TITLE Marvin Kuschner Professor and Chairman Department of Pathology Stony Brook Medicine		
eRA COMMONS USER NAME SHROYER.KEN			
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Colorado College, Colorado Springs, CO	B.A.	1978	Biology
Univ. of CO Graduate School, Denver, CO	Ph.D.	1983	Experimental Pathology
Univ. of CO School of Medicine, Denver, CO	M.D.	1987	Medicine

### A. Personal Statement

Dr. Shroyer is Board Certified in Anatomic and Clinical Pathology (1991), with subspecialty certification in Cytopathology (1995). He is an experienced surgical pathologist and cytopathologist and has also maintained continuous federally-funded grant support since 1993. He was a member of the graduate school at the University of Colorado Health Sciences Center for more than 15 years and has been a member of the Molecular Biology Program at Stony Brook University since 2007. He has trained more than 40 graduate students, medical students, MSTP students, residents, and clinical fellows, many of whom have gone on to complete postdoctoral research fellowships, including some that now hold faculty positions in the United States, Europe and Japan. Dr. Shroyer's research has focused on the molecular characterization of benign, premalignant, and malignant lesions of the female genital tract and a wide range of other anatomic sites. He invented the method of DNP labeling of nucleic acid probes, was a pioneer in the development of methods for *in situ* hybridization of mRNAs in the early 1980s, and was the first to report the analysis of x-chromosome inactivation in archival tissues as a marker of clonality. His laboratory has developed and evaluated the expression of numerous novel molecular assays of cellular immortalization and malignant transformation, including telomerase, HPV, surviving, p16, and B7-H4, using PCR-based methods, immunohistochemistry, and *in situ* hybridization.

### B. Positions and Honors

#### Positions and Employment:

1987-1988	Intern in Anatomic and Clinical Pathology, University of Colorado Health Sciences Center
1988-1991	Resident in Anatomic and Clinical Pathology, Univ. of Colorado Health Sciences Center
1991	Chief Resident in Pathology, University of Colorado Health Sciences Center
1991-1997	Assistant Professor of Pathology, University of Colorado Health Sciences Center
1997-2001	Associate Professor with tenure, University of Colorado Health Sciences Center
2002-2007	Professor with tenure, University of Colorado Health Sciences Center
1991-2007	Graduate Faculty, University of Colorado Health Sciences Center, Graduate School
1993-2007	Director of Cytopathology, University of Colorado Health Sciences Center
2000-2007	Director of Surgical Pathology, University of Colorado Health Sciences Center
2007-present	Marvin Kuschner Professor and Chair, Department of Pathology, Stony Brook University Medical Center, State University of New York
1991-present	Graduate Faculty, Stony Brook University Medical Center, Molecular and Cellular Biology Program

### **Other Experience and Professional Memberships (selected):**

- 2004- Editorial Board, Human Pathology
- 2006- Associate Editor, Journal of Clinical Virology
- 2001- National Cancer Institute Study Section member, including IMAT, Applied Emerging Technologies for Cancer Research, Alliance of Glycobiologists for Detection of Cancer and Cancer Risk, SPOREs in Breast, Cervical, Endometrial, Ovarian, Skin Cancers, Lymphoma, Genitourinary, and Gastrointestinal Cancers and In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- 1991- United States and Canadian Academy of Pathology (Member of the Scientific Advisory Board)
- 1991- American Association for Cancer Research
- 1993- American Society of Cytopathology
- 2002- American Society for Investigative Pathology

### **Honors (selected):**

- 1985-1987 Edgar and Marion Adler Scholar Award, UCHSC
- 1987 Joseph and Regina Glaser Student Research Award, UCHSC
- 1991 Robert H. Fennell, Jr., M.D. Award, Department of Pathology, UCHSC
- Lucien J. Rubinstein Award for the Best Paper on Neuro-oncology. Shared with B.K. Kleinschmidt-DeMasters and M.A. Bitter. The American Association of Neuropathologists

### **Invention (selected):**

Regulation of B7-H4 Expression by miR-34 and its Clinical Utility  
 Stony Brook University Research Foundation Reference Number: R-8128  
 Co-Inventor with Jingfang Ju  
 Disclosure Date: 9/11/2008

### **C. Contribution to Science**

Over the course of my career as a physician/scientist, my research has been focused on the identification and validation of objective molecular approaches to improve diagnostic accuracy in surgical pathology and cytopathology. The ultimate aim of this research has been to provide pathologists with objective molecular markers of cancer that can be integrated and interpreted in the context of tissue histopathology and cytopathology. My initial research focused on the development of methods to define tissue clonality and immortalization, based respectively on the development of methods to define patterns of X-chromosome inactivation in archival microdissected specimens and on the analysis of telomerase expression. These studies contributed to the recognition that epithelial premalignant lesions of the female genital tract are composed of immortalized populations of cells, with key characteristics that overlap with those of invasive carcinoma.

A second major aim has been to identify cancer biomarkers that could be used to improve diagnostic accuracy for premalignant and malignant clinical tissue specimens. My lab pioneered early studies of p16 as a cervical cancer biomarker and was the first to deploy p16 testing as a marker used in Pathology diagnostic laboratories to improve diagnostic accuracy. This work subsequently was expanded to include the analysis of p16, MCMs, and other molecular markers of cervical cancer that could be applied to cervical cytology specimens, with the underlying of improving diagnostic accuracy of the Pap test. Most recently, my lab utilized mass spectrometry of laser capture microdissected tissue specimens and identified keratin 17 (K17) as prognostic biomarker predict patient survival, independent of tumor grade and stage.

## **Research Papers (selected)**

1. Keratin 17 in premalignant and malignant squamous lesions of the cervix: proteomic discovery and immunohistochemical validation as a diagnostic and prognostic biomarker. Escobar-Hoyos LF, Yang J, Zhu J, Cavallo JA, Zhai H, Burke S, Koller A, Chen EI, **Shroyer KR**. Mod Pathol. 2014 Apr;27(4):621-30. Epub 2013 Sep 20. PMID: 24051697
2. Immunohistochemical localization of HE4 in benign, borderline, and malignant lesions of the ovary. Georgakopoulos P, Mehmood S, Akalin A, **Shroyer KR**. Int J Gynecol Pathol. 2012 Nov;31(6):517-23. PMID: 23018214
3. Immunocytochemical colocalization of P16(INK4a) and Ki-67 predicts CIN2/3 and AIS/adenocarcinoma. Singh M, Mockler D, Akalin A, Burke S, Shroyer A, **Shroyer KR**. Cancer Cytopathol. 2012 Feb 25;120(1):26-34. PMID: 22162342
4. B7-H4 overexpression in ovarian tumors. Tringler, B, Liu W, Corral L, Torkko KC, Enomoto T, Davison S. Lucia MS, Heinz DE, Papkoff J, **Shroyer, KR**. Gynecol Oncol. 2006 Jan;100(1):44-52. Epub 2005 Oct 26. PMID: 16256178

## **Complete List of Published Work in MyBibliography:**

<http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/47427615/>

## **D. Research Support**

### **Active**

Department of Veterans Affairs Merit Review (Zucker) 10/01/09-09/30/13, 0.6 months  
 Reversibility of Epithelial Mesenchymal Transition in Prostate Cancer.  
 Kenneth R. Shroyer, Co-I

Department of Defense. (Sitharaman) 2009-2011  
 Tumor-targeting single-wall carbon nanotubes for microwave-based imaging and hyperthermia treatment of breast cancer: A small animal study.  
 Kenneth R. Shroyer, Consultant

NIH 1R33CA140084. (Robinson, Shroyer: Subcontract PI) 04/01/11-03/31/15, 0.6 months  
 Specific Detection of Cervical Cancers Using Cytometry-Based Molecular Diagnostics.

Coulter Foundation. Pre-clinical Evaluation of Carbon (Balaji Sitharaman) 2011-2013  
 Nanostructure-Based High-Performance Contrast Agent for Magnetic Resonance Imaging.  
 Kenneth R. Shroyer, Co-I

### **Completed**

Carol M. Baldwin Breast Cancer Research Award (Sitharaman) 11/03/08-11/02/09 0.6 months  
 Multifunctional Carbon Nanostructure-Based Platforms for Breast Cancer Theragnostics.  
 Kenneth R. Shroyer, Co-I

TRO Program, Proteomics Developmental Projects Award (Shroyer) 2009-2010  
 Identifying Biomarkers for Pre-malignant and Invasive Cervical Cancer.  
 Kenneth R. Shroyer, PI

TRO Program, Carol M. Baldwin Breast Cancer Research Award (Nemesure) 2009-2010  
 Evaluation of a Newly Designed Device for Breast Cancer Screening.  
 Kenneth R. Shroyer, Co-I

NIH/NCI 4R33CA110519-02 (Shroyer) 07/01/05-04/30/10 1.80 months  
R33 phased innovation and application award p16 and HPV in low-grade cervical cytologic specimens.  
Kenneth R. Shroyer, PI

Carol M. Baldwin Breast Cancer Research Award (Sitharaman) 11/03/08-11/02/09  
(Targeted Research Opportunities)  
Multifunctional Carbon Nanostructure-Based Platforms for Breast Cancer Theragnostics.  
Kenneth R. Shroyer, Co-I

Proteomics Developmental Projects Award (Kew) 11/03/08-11/02/09, 0.6 months  
Kenneth R. Shroyer, Co-I

Targeted Research Opportunities, Proteomics Developmental Projects Award (Kew) 11/03/08-11/02/09  
Kenneth R. Shroyer, Co-I

RCA125370A (Robinson) 01/01/07-12/31/08  
Specific Biomarkers for Detection of Cervical Cancer Cells Using Flow Cytometry score.  
Kenneth R. Shroyer, Consultant

National Cancer Institute, R21 (Shroyer) 08/01/04-06/30/08  
Phased innovation and application award. p16 and HPV in low-grade cervical cytologic specimens.  
Kenneth R. Shroyer, PI

## RESEARCH &amp; RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator				
Prefix:	First Name*: Mark	Middle Name	Last Name*: Stewart	Suffix:
Position/Title*:	Professor, Dean Sch Grad Stud			
Organization Name*:	The Research Foundation for SUNY, Downstate Medical Center			
Department:	Physiology and Pharmacology			
Division:	Graduate Studies			
Street1*:	450 Clarkson Ave			
Street2:				
City*:	Brooklyn			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	112032012			
Phone Number*:	718-270-1167	Fax Number:	718-270-3103	E-Mail*: mark.stewart@downstate.edu
Credential, e.g., agency login: mstewart				
Project Role*: Other (Specify)			Other Project Role Category: Project Lead	
Degree Type:			Degree Year:	
Attach Biographical Sketch*:			File Name	
Attach Current & Pending Support:			Stewart_biosketch0315_P20.pdf	

PROFILE - Senior/Key Person				
Prefix:	First Name*: Ellen	Middle Name	Last Name*: Li	Suffix:
Position/Title*:	Chief			
Organization Name*:	The Research Foundation for SUNY, Stony Brook University			
Department:	Medicine			
Division:	Gastroenterology Hepatology			
Street1*:	101 Nicolls Road-Health Sciences Center			
Street2:	T-17 Room 060			
City*:	Stony Brook			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117948173			
Phone Number*:	631-444-2119	Fax Number:	631-444-8886	E-Mail*: ellen.li@stonybrook.edu
Credential, e.g., agency login: ELLENLI1				
Project Role*: Co-Investigator		Other Project Role Category:		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:				
Attach Current & Pending Support:				

PROFILE - Senior/Key Person				
Prefix:	First Name*: Patricia	Middle Name Ann	Last Name*: Thompson	Suffix:
Position/Title*:	Professor			
Organization Name*:	Stony Brook university			
Department:	Pathology			
Division:				
Street1*:	Department of Pathology			
Street2:	Associate Director of Basic Science			
City*:	Stony Brook			
County:				
State*:	NY: New York			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	117940000			
Phone Number*:	631-444-6818	Fax Number:		E-Mail*: patricia.thompson-carino@stonybrookmedicine.edu
Credential, e.g., agency login: pthompson				
Project Role*: Co-Investigator		Other Project Role Category:		
Degree Type: PHD,BS		Degree Year:		
		File Name		
Attach Biographical Sketch*:		Thompson_Bio_LiP20.pdf		
Attach Current & Pending Support:				

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2015

End Date\*: 08-31-2016

Budget Period: 1

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Patricia		Thompson		Co-Investigator	183,300.00	0.3			4,583.00	2,608.00	7,191.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons:		File Name:									Total Senior/Key Person	7,191.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
					Total Salary, Wages and Fringe Benefits (A+B)		7,191.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
--------------------------	-------------

**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	500.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	12,000.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
<b>Total Other Direct Costs</b>	<b>12,500.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>19,691.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	58.0	7,691.00	4,461.00
2. Down State MTDC	61.5	12,000.00	7,380.00
<b>Total Indirect Costs</b>			<b>11,841.00</b>
<b>Cognizant Federal Agency</b>	Modified Total Direct Cost rate, Agreement dated 2/21/2014 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>31,532.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: Ed_and_Training_Just.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 2

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2016

End Date\*: 08-31-2017

Budget Period: 2

## A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Patricia		Thompson		Co-Investigator	183,300.00	0.3			4,583.00	2,608.00	7,191.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons:		File Name:									Total Senior/Key Person	7,191.00

## B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	Total Number Other Personnel					Total Other Personnel	0.00
Total Salary, Wages and Fringe Benefits (A+B)							7,191.00

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

0.00

2. Foreign Travel Costs

0.00

<b>Total Travel Cost</b>	<b>0.00</b>
--------------------------	-------------

**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

0.00

2. Stipends

0.00

3. Travel

0.00

4. Subsistence

0.00

5. Other:

**0 Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	500.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	12,000.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
<b>Total Other Direct Costs</b>	<b>12,500.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>19,691.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	58.0	7,691.00	4,461.00
2. Downstate MTDC	61.5	12,000.00	7,380.00
<b>Total Indirect Costs</b>			<b>11,841.00</b>
<b>Cognizant Federal Agency</b>	Modified Total Direct Cost rate, Agreement dated 2/21/14 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>31,532.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: Ed_and_Training_Just.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 3

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project    ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 3

**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Patricia		Thompson		Co-Investigator	183,300.00	0.3			4,583.00	2,608.00	7,191.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												
<b>Additional Senior Key Persons:</b> File Name:											<b>Total Senior/Key Person</b>	<b>7,191.00</b>

**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
<b>0</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>0.00</b>
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>							<b>7,191.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
------------------------------------------------------------------------	------

2. Foreign Travel Costs	0.00
-------------------------	------

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
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2. Stipends	0.00
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3. Travel	0.00
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4. Subsistence	0.00
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5. Other:	
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<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	500.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	12,000.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
<b>Total Other Direct Costs</b>	<b>12,500.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>19,691.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	58.0	7,691.00	4,461.00
2. Down State MTDC	61.5	12,000.00	7,380.00
	<b>Total Indirect Costs</b>		<b>11,841.00</b>
<b>Cognizant Federal Agency</b>	Modified Total Direct Cost rate, Agreement dated 2/21/14 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>31,532.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: Ed_and_Training_Just.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 4

ORGANIZATIONAL DUNS\*: 8048782470000

Budget Type\*: ☒ Project    ☐ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Stony Brook University

Start Date\*: 09-01-2018

End Date\*: 08-31-2019

Budget Period: 4

**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Patricia		Thompson		Co-Investigator	183,300.00	0.3			4,583.00	2,608.00	7,191.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												
<b>Additional Senior Key Persons:</b> File Name:											<b>Total Senior/Key Person</b>	<b>7,191.00</b>

**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
<b>0</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>0.00</b>
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>							<b>7,191.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	0.00
------------------------------------------------------------------------	------

2. Foreign Travel Costs	0.00
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<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance	0.00
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2. Stipends	0.00
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3. Travel	0.00
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4. Subsistence	0.00
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5. Other:	
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<b>0 Number of Participants/Trainees</b>	<b>Total Participant Trainee Support Costs</b>	<b>0.00</b>
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RESEARCH &amp; RELATED Budget {C-E} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 8048782470000**Budget Type\*:** ☒ Project ☐ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Stony Brook University**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	500.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	12,000.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
<b>Total Other Direct Costs</b>	<b>12,500.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>19,691.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. Modified Total Direct Costs	58.0	7,191.00	4,461.00
2. Down State MTDC	61.5	12,000.00	7,380.00
<b>Total Indirect Costs</b>			<b>11,841.00</b>
<b>Cognizant Federal Agency</b>	Modified Total Direct Cost rate, Agreement dated 2/21/14 with		
(Agency Name, POC Name, and POC Phone Number)	Department of Health and Human Services, Darryl W. Mayes,		
	212-264-2069		

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>31,532.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
	<b>0.00</b>

<b>K. Budget Justification*</b>	File Name: Ed_and_Training_Just.pdf
	(Only attach one file.)

RESEARCH &amp; RELATED Budget (F-K) (Funds Requested)

## Budget Justification – Training and Education (Institutional)

### A. Key Personnel:

Patricia Thompson, Ph.D, contact PI. **Dr. Thompson** will devote 0.3 calendar month to this project at the NIH cap salary and fringes. **Dr. Thompson** is Professor of Pathology and Associate Director of Basic Research at the Stony Brook Cancer Center and was recently recruited from the Arizona Cancer Center. She was co-PI of a Komen postgraduate training program on health disparities in breast cancer at the Arizona Cancer Center. She will work closely with Dr. Tsirkas who is the founding Director of the Stony Brook Scholars in Biomedicine program to expand this program to a total of 9 from 5 slots with an additional focus on conducting translational research on cancer health disparities. She will work closely with **Drs. Salifu** and **Stewart** (Downstate) and with **Dr. McCombie** (CSHL) to plan the development of teaching modules on Cancer Health Disparities aimed at the trainees in the Scholars in Biomedicine in Cancer Health Disparities, and to also develop workshops designed to increase awareness of cancer health disparities among established cancer research investigators.

**B. Other Personnel:** none

**C. Equipment:** none.

**D. Supplies:** none

**E. Travel:** none

### F. Other Expenses:

Subcontract: \$12,000 to SUNY Downstate for holding an annual symposium/workshop on Cancer Health Disparities held at the Brooklyn Center of Health Disparities located on the SUNY Downstate campus.

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	Totals (\$)	
Section A, Senior/Key Person		28,764.00
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		28,764.00
Section C, Equipment		0.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		50,000.00
1. Materials and Supplies	2,000.00	
2. Publication Costs	0.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	48,000.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	0.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		78,764.00
Section H, Indirect Costs		47,364.00
Section I, Total Direct and Indirect Costs (G + H)		126,128.00
Section J, Fee		0.00

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 1

ORGANIZATIONAL DUNS\*: 0407963280000

**Budget Type\*:**    ☐ Project    ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Mark		Stewart		Co-I		0.6			0.00	0.00	0.00
2.	Moro		Salifu		PD/PI		0.3			0.00	0.00	0.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												
<b>Additional Senior Key Persons:</b> File Name:											<b>Total Senior/Key Person</b>	<b>0.00</b>

**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
<b>0</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>0.00</b>
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>							<b>0.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2015**End Date\*:** 08-31-2016**Budget Period:** 1

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	1,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Training Program	11,000.00
<b>Total Other Direct Costs</b>	<b>12,000.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>12,000.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. MTDC	61.5	12,000.00	7,380.00
	<b>Total Indirect Costs</b>		<b>7,380.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>19,380.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: P20_grant- Budget_justification_Education- Training_Core_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 2

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project    ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2016

End Date\*: 08-31-2017

Budget Period: 2

**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Mark		Stewart		Co-I		0.6			0.00	0.00	0.00
2.	Moro		Salifu		PD/PI		0.3			0.00	0.00	0.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												
<b>Additional Senior Key Persons:</b> File Name:											<b>Total Senior/Key Person</b>	<b>0.00</b>

**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
<b>0</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>0.00</b>
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>							<b>0.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>0.00</b>
--------------------------	-------------

**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2016**End Date\*:** 08-31-2017**Budget Period:** 2

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	1,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Training Program	11,000.00
<b>Total Other Direct Costs</b>	<b>12,000.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>12,000.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. MTDC	61.5	12,000.00	7,380.00
		<b>Total Indirect Costs</b>	<b>7,380.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>19,380.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>

<b>K. Budget Justification*</b>	File Name: P20_grant- Budget_justification_Education- Training_Core_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 3

ORGANIZATIONAL DUNS\*: 0407963280000

Budget Type\*: ☐ Project    ☒ Subaward/Consortium

Enter name of Organization: The Research Foundation for SUNY, Downstate Medical Center

Start Date\*: 09-01-2017

End Date\*: 08-31-2018

Budget Period: 3

**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Mark		Stewart		Co-I		0.6			0.00	0.00	0.00
2.	Moro		Salifu		PD/PI		0.3			0.00	0.00	0.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												
<b>Additional Senior Key Persons:</b>		File Name:		<b>Total Senior/Key Person</b>								<b>0.00</b>

**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
<b>0</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>0.00</b>
						<b>Total Salary, Wages and Fringe Benefits (A+B)</b>	<b>0.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>0.00</b>
--------------------------	-------------

**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2017**End Date\*:** 08-31-2018**Budget Period:** 3

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	1,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Training Program	11,000.00
<b>Total Other Direct Costs</b>	<b>12,000.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>12,000.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. MTDC	61.5	12,000.00	7,380.00
		<b>Total Indirect Costs</b>	<b>7,380.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>19,380.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: P20_grant- Budget_justification_Education- Training_Core_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## RESEARCH &amp; RELATED BUDGET - SECTION A &amp; B, BUDGET PERIOD 4

ORGANIZATIONAL DUNS\*: 0407963280000

**Budget Type\*:**    ☐ Project    ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4**A. Senior/Key Person**

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Mark		Stewart		Co-I		0.6			0.00	0.00	0.00
2.	Moro		Salifu		PD/PI		0.3			0.00	0.00	0.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												
<b>Additional Senior Key Persons:</b> File Name:											<b>Total Senior/Key Person</b>	<b>0.00</b>

**B. Other Personnel**

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
<b>0</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>0.00</b>
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>							<b>0.00</b>

RESEARCH &amp; RELATED Budget {A-B} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
----------------	-----------------------

**Total funds requested for all equipment listed in the attached file**

<b>Total Equipment</b>	<b>0.00</b>
------------------------	-------------

**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)\***

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

<b>Total Travel Cost</b>	<b>0.00</b>
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**E. Participant/Trainee Support Costs****Funds Requested (\$)\***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

**Number of Participants/Trainees****Total Participant Trainee Support Costs****0.00**

RESEARCH &amp; RELATED Budget (C-E) (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4****ORGANIZATIONAL DUNS\*:** 0407963280000**Budget Type\*:** ☐ Project ☒ Subaward/Consortium**Enter name of Organization:** The Research Foundation for SUNY, Downstate Medical Center**Start Date\*:** 09-01-2018**End Date\*:** 08-31-2019**Budget Period:** 4

<b>F. Other Direct Costs</b>	<b>Funds Requested (\$)*</b>
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	1,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Training Program	11,000.00
<b>Total Other Direct Costs</b>	<b>12,000.00</b>

<b>G. Direct Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>	<b>12,000.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1. MTDC	61.5	12,000.00	7,380.00
		<b>Total Indirect Costs</b>	<b>7,380.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>	<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>19,380.00</b>

<b>J. Fee</b>	<b>Funds Requested (\$)*</b>
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<b>K. Budget Justification*</b>	File Name: P20_grant- Budget_justification_Education- Training_Core_2015.pdf (Only attach one file.)
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RESEARCH &amp; RELATED Budget {F-K} (Funds Requested)

## **Feasibility Studies to Build Collaborative Partnerships in Cancer Research (P20)**

### **Feasibility studies to build collaborative partnerships in reducing racial/ethnic disparities in GI cancer research**

#### **BUDGET JUSTIFICATION – Administrative Core**

##### **PERSONNEL**

Moro Salifu, MD, MBA, MPH: Principal Investigator (0.6 calendar months, 5% effort (in-kind), Years 1-4)

Dr. Salifu, Professor of Medicine, is the Chair of the Department of Medicine and Chief of the Division of Nephrology. Dr. Salifu also is the Director of the Brooklyn Health Disparities Center (BHDC) and Principal Investigator of the P20 grant supporting the expansion of activities of the BHDC. Dr. Salifu will be involved with the Administrative Core of the overall project.

Yalini Senathirajah, PhD: Co-Investigator (0.3 calendar months, 2.5% effort, Years 1-4)

Dr. Senathirajah, Assistant Professor, is in the Department of Medical Informatics within the College of Health Related Professions. Dr. Senathirajah will be involved with the clinical data integration to create a shared resource that can be utilized for downstream research analysis in collaboration with Dr. Joel Saltz at Stony Brook.

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	Totals (\$)	
Section A, Senior/Key Person		0.00
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		0.00
Section C, Equipment		0.00
Section D, Travel		0.00
1. Domestic	0.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		48,000.00
1. Materials and Supplies	0.00	
2. Publication Costs	0.00	
3. Consultant Services	4,000.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	44,000.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		48,000.00
Section H, Indirect Costs		29,520.00
Section I, Total Direct and Indirect Costs (G + H)		77,520.00
Section J, Fee		0.00

## PHS 398 Cover Page Supplement

OMB Number: 0925-0001

## 1. Project Director / Principal Investigator (PD/PI)

Prefix:

First Name\*: Mark

Middle Name:

Last Name\*: Stewart

Suffix:

## 2. Human Subjects

Clinical Trial?      ☒ No      ☐ YesAgency-Defined Phase III Clinical Trial?\*      ☐ No      ☐ Yes

## 3. Permission Statement\*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes      ☐ No

## 4. Program Income\*

Is program income anticipated during the periods for which the grant support is requested?      ☐ Yes      ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount (\$)*	Source(s)*
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

## PHS 398 Cover Page Supplement

### 5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?\*      ☒ No      ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: [http://grants.nih.gov/stem\\_cells/registry/current.htm](http://grants.nih.gov/stem_cells/registry/current.htm). Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s):      ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

### 6. Inventions and Patents (For renewal applications only)

Inventions and Patents\*:      ☐ Yes      ☐ No

If the answer is "Yes" then please answer the following:

Previously Reported\*:      ☐ Yes      ☐ No

### 7. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name\*:

Middle Name:

Last Name\*:

Suffix:

☐ Change of Grantee Institution

Name of former institution\*:

## PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	P20Introduction_Training_Education_031915.pdf
2. Specific Aims	SpecificAims_Train.pdf
3. Research Strategy*	Research_Strategy_TE.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	
6. Inclusion of Women and Minorities	
7. Inclusion of Children	
Other Research Plan Sections	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	Train_Edu_LOS.pdf
13. Resource Sharing Plan(s)	ResourceSharingPlanTraining_031915_eli.pdf
Appendix (if applicable)	
14. Appendix	

## INTRODUCTION – TRAINING AND EDUCATION

We appreciate the reviewer concerns regarding the training and education program and agree that it lacked sufficient detail and was underdeveloped overall. As part of our ongoing efforts to build the program since the prior review, we have completely revised the training and education program. We believe that we have addressed the concerns raised in the previous review including low innovation in the training component and generally a lack of detail. We have significantly strengthened the training and education program leadership, better integrated the collective strengths of the three partner institutions and we believe, developed a highly innovative strategy in our training and education program. Overall, we believe that the training and education component of our P20 planning grant is significantly improved as a result of the reviewer contribution and the time that we have had since the prior submission to work together to further develop our plan and to think more creatively about how to achieve our training and education goals. In this revised planning grant submission entitled “Partnership to Study Racial/Ethnic Differences in GI Cancer Biology” in response to PAR-14-152, we have made many changes in response to the reviewers’ thoughtful comments. Specifically, **Dr. Patricia Thompson**, recently recruited to the Stony Brook Cancer Center as Associate Director of Basic Research, has joined the leadership for this program. We have also changed the composition of the Internal Advisory Committee which is now co-chaired by Dr. Thompson and Dr. Alea Mills, who Director of the NCI T32 CSHL Cancer Gene Discovery and Cancer Biology Postdoctoral Research Training Grant. Finally we have added an External Advisory Board, which includes Dr. Marilyn Fraser-White, Deputy Executive Director for the Arthur Ashe Institute for Urban Health (<http://www.arthurasheinstitute.org/arthurashe/about/>). Dr. Fraser-White has been engaged in development and implementation of health disparities learning modules for high school students and community based organizers.

Reviewers raised the issue of whether or not we should consider creating a separate graduate program as opposed to leveraging our existing graduate and training activities. We debated this suggestion at some length and with input from our advisors. Part of the challenge is to not compete amongst our existing strong programs for exceptional students but to enhance diversity within them. An issue for us to successfully attract, train and retain the best and the brightest of students from underrepresented and underserved communities is to provide the best academic research environment for URM students that motivates them. As such, we don’t wish to detract from our already exceptional graduate training programs but make these programs more attractive to URM students and to do so in a way that they want to stay in academic science. As such, we opted for a hybrid model for the graduate training piece. Specifically, in dialogue, we decided to take advantage of the graduate level translational research Scholars in Biomedical Sciences (SBMS) training program existing at SUNY Stony Brook and build into it a focus in cancer health disparities (C-HD). We were able to secure institutional resources to support additional funded, competitive slots into the C-HD track for graduate students from all three institutions. This program will build on an existing SUNY Stony Brook SBMS certificate program, which is designed to help graduate students obtain the skills to partner with clinicians and clinician scientists in the application of emerging biological knowledge to medical practice. Pilot project affiliated graduate students will propose a translational project, in our case addressing C-HD, and will be jointly mentored by a research mentor and a clinical co-mentor. Translational projects that represent collaborative projects between at least two of the three institutions (SUNY Stony Brook, SUNY Downstate and CSHL), and students from diverse backgrounds will be given high priority. We anticipate that with the strength and depth of our existing graduate programs the SBMS-CHD program will attract talented underrepresented minority students, who have personal interests in addressing cancer health disparities. By partnering clinical mentors with research mentors in this program, we also hope to catalyze the development of additional translational fusion projects addressing cancer-related health disparities. Importantly, this strategy was incredibly well received by the program directors of our existing graduate programs across the institutions and existing training grant programs. While there remains a bit of heavy lifting to implement this strategy, we believe that it is innovative, collaborative and in time will be highly attractive to URM students seeking graduate degrees in biomedical science. We believe that this will position us to create a national model that integrates social identity and early career motivators into the training of future graduate students in cancer research and bring the best and the brightest together into a group-supporting cohort of students that will sustain their trajectory towards tier one research institutions as independent cancer research faculty.

Because the application is so significantly revised, there is no demarcation of new text.

## TRAINING AND EDUCATION PROGRAM

### 1. SPECIFIC AIMS

#### 1.1. Rationale for a Partnered Training and Education Program in Cancer Health Disparities (CHDs).

In theory, the practice of oncology that is informed by ‘omics’ or Precision Oncology is the ability to tailor patient treatment to specific molecular targets/characteristics present to improve drug effectiveness and patient outcomes at the patient level. This contrasts with the traditional approach of treatment based on population level responsiveness. As a consequence of improved predictiveness of patient-level benefit, ‘precision oncology’ further holds promise to reduce toxicities and costs of ineffective treatment strategies through the use of biomarker indicators of responder and non-responder phenotypes prior to (tumor biomarker) or early (e.g., imaging biomarkers) during treatment initiation. This progress, while highly exciting, is occurring despite unclear generalizability across diverse populations, data on impact to drug development and delivery costs and with no attention to the inevitable lag to community practice. As such, a gross lack of diversity in ongoing genomics research both in terms of patient populations and the persistent low workspace diversity in cancer research are well poised to deepen the already large disparity in cancer outcomes across populations. The ability to generalize advances in cancer omics in a timely fashion to all patients depends on an understanding of how underlying population differences affect tumor biology, cancer behavior in the clinic and treatment responsiveness. Thus, the full impact of the promise of ‘precision oncology’ will *only* be achieved when advances in care are effectively translated from academic centers to community practice. The integration of faculty, fellows and students from underrepresented and medically underserved communities (URM) in the research workforce *with* efforts to enhance awareness of health disparities in our research faculty and mentors *are jointly needed* to identify, study and solve issues of CHD.

Individually, our institutions have exceptional strengths in computational science and molecular and cellular biology of cancer (SBU), graduate and medical education for students from underserved/underrepresented backgrounds with excellence in health disparities education (Downstate) and world-renowned cancer biology and ‘omics’ technologies (CSH). Capitalizing on our strengths, we propose to address critical research and translation gaps for CHDs by leveraging our strengths through a unique ‘Scholars in Biomedical Sciences for CHDs’ program (SBMS-CHD). The overarching goal and we believe a major solution to address CHDs is to successfully train PhD and MD/PhD scientists in cancer research that integrates concepts of research translation from the ‘bench-to-bedside’ academic model to cancer care delivery in community practice. The specific goal of this planning period will be to develop and test the effectiveness of a training environment aimed at enhancing knowledge of CHDs among established faculty mentors and to engage and empower, through knowledge and training in CHDs, a cohort of exceptional cancer research scientists with an interest in conducting high-quality research aimed at addressing biological and clinical causes of CHDs.

**AIM 1. To develop a SBMS-CHD training program for outstanding graduate students that emphasizes the bench to community cancer care delivery continuum.**

Specifically, we propose to leverage the strengths of our existing training infrastructures to create a training track for graduate students interested in basic or translational cancer research coupled to a didactic, facilitated and experienced-based exposure to health disparities in the cancer continuum. The overarching objective of this aim is to engage our existing pool of excellent MD and MD/PhD cancer scientist trainees from all backgrounds to gain knowledge of CHDs. A specific objective of the program is to create a high-quality research training environment that enhances knowledge of CHDs globally in our students and that facilitates the development of hypothesis-based research aimed at addressing and eradicating causes of CHD.

**AIM 2. To enhance the research capacities, knowledge and diversity among our cancer research faculty and fellows with research interest in CHD.**

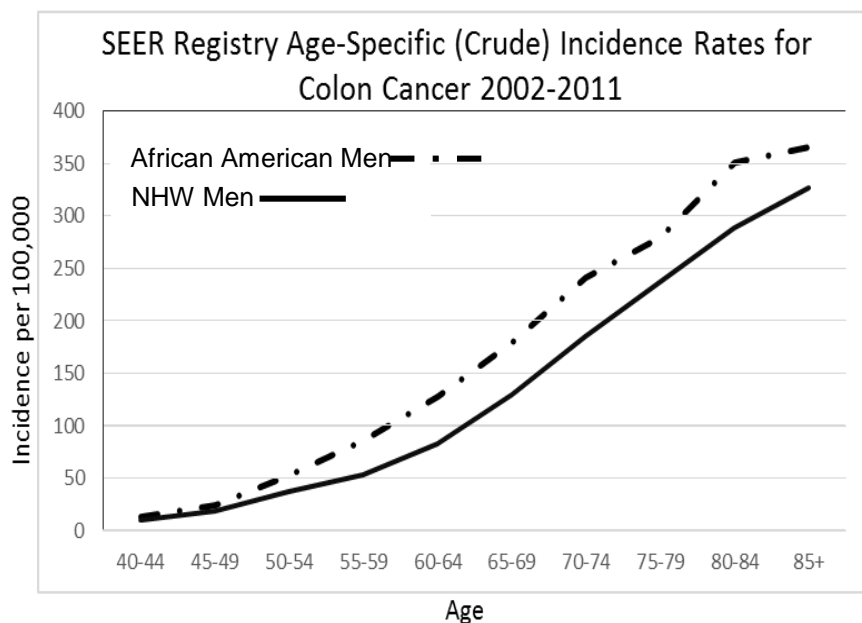
Emphasis will be placed on building mentorship capacity to increase successful competition of our URM faculty and fellows in peer review publication and funding via exceptional and impactful cancer research activities. The overarching objective of this aim is to develop cross-cultural competency in the research workspace. This will include enhancing our research mentors’ awareness of the need to conduct and translate cancer research aimed addressing CHDs. An important component of this effort will be to enhance our mentored training environment, through institutional partnerships, for graduate students, early career faculty and fellows from underrepresented and underserved communities to increase their professional success and impact.

**1.2. Impact.** Success of our effort will be the creation of a unique training environment to address CHD.

## TRAINING AND EDUCATION - RESEARCH STRATEGY

### 1. Significance.

**1A. Population Diversity and Cancer Health Disparities – Cause(s).** Disparities in cancer outcomes among patient populations of different race, educational and socioeconomic (SES) backgrounds are well-documented (1-9). The disparities between patient groups pose significant challenges to the U.S. healthcare system, the economic health of the country and, for the individual cancer patient and their families, are emotionally and financially devastating. Health disparities, and herein, cancer-related health disparities (C-HDs), are rooted in numerous causes (10-13). These include those that derive from poverty and lack of educational opportunities and those that derive from cultural and biological diversity that exists between populations. Importantly, there are a number of examples where it is the joint effects of factors that some of the most notable C-HDs exists (breast, prostate, and colon cancers).



An example, specific to our research interest in GI cancers and C-HD is the high rate of aggressive cancers arising in the colon of AA men and occurring at younger ages (14). The age-specific incidence of colon cancer per 100,000 individuals is higher for African American (AA) men and exhibits a 5 to 10 year earlier age-related increase when compared to non-Hispanic Whites (NHW) (Figure 1) – **the latter being the population on which age to initiate colon cancer screening are based** (15). This alone likely explains part of the higher stage at presentation among AA men when age-matching.

Numerous studies aimed at determining whether differences in colorectal cancer (CRC) screening rates between AA and NHWs explain disparate outcomes have

yielded variable results. In some studies, CRC screening rates among AAs are reported to be lower than their NHW counterparts (16) (17-20), particularly if the screening modality is colonoscopy (21) and when one considers geographic factors (i.e., Southern versus Northeastern and Western states)(22). However, in more recent and well-controlled studies, the actual screening rates among AA were found to be fairly similar to NHWs (23) – though screening initiated at age 50 years likely explaining the higher stage at presentation among AA men (15). Notable though, despite efforts to reach screening equality, AA men exhibit higher incidence of colon cancer at an earlier age, have higher overall mortality and when matched on stage of diagnosis and treatment, experience worse CRC specific outcomes across most studies. These observations underlie the hypothesis that molecular differences at the tumor level between AA and NHWs partly explain differences in the rate of tumor growth (age of onset earlier) and propensity to metastasize (stage at diagnosis is late). And that biologic heterogeneity explains part of the disparity in incidence and outcomes of colon cancer observed for AA when compared to NHWs.

This example of colon cancer illustrates very clearly how numerous factors give rise to disparate outcomes among patients of different race, ethnic and social backgrounds. And while we more often hear the words ‘not generalizable to all populations’ and population heterogeneity with ‘funding prioritization’, far too few basic and translational researchers understand or appreciate the impact of population heterogeneity on how discoveries made in cancers derived from one population impacts the translation of their discoveries to effective prevention, diagnosis and treatment. **It is this lack of knowledge among the cancer biology community whereby C-HDs continue to be relegated largely to the social and behavioral sciences with the cancer biologist thinking one size fits all – a mindset that limits the potential for impact to prevent, diagnosis and treat cancers across diverse populations. This is a significant gap in knowledge among the cancer research community.**

**1B. Cancer Research Workspace Diversity to Address Cancer Health Disparities.** Despite quite extensive efforts to increase diversity generally among the biomedical research environment, including the cancer research workspace, recent studies suggest that all groups (URM and women from well-represented (WM) racial/ethnic backgrounds) were less interested in research faculty careers as their graduate training progressed when compared WR-men with URM women the least interested in research based faculty careers (24). We believe that an important aspect of enhancing the impact of basic and translation cancer biology needed to address disparities in cancer depends strongly on increasing representation of diverse backgrounds among scientists in the cancer research workspace. Social identity is as an important component of an individual's values and motivations and underlies the benefits that diversity brings to problem solving. This is the rationale for concerted efforts to support and enhance representation of individuals from underserved and underrepresented communities into the basic sciences and in graduate biology programs across the country. URM investigators are thought to bring experiences and community identification that provide them with unique perspectives that influence their approach to solving scientific questions and that uniquely motivate their decision-making in their career paths. While there has been some modest success, overall URM representation among tier 1 academic research institutions as federally funded investigators remains low and worse, increasingly undesirable. A number of barriers to successful competition for federal funding have been identified. These include inadequate research infrastructure for training and development as well as lack of ability to conduct data analysis and importantly, a lack of training and career development throughout the early educational pipeline (24, 25). We believe that an important factor that is underappreciated in the equation, which we and others (24) have begun to identify among trainees, lies specifically in failing to incorporate factors of social identity that motivated young people to enter the research domain, particularly to serve the needs of their community. An example from Gibbs et al., (26) 'What do I want to be with my PhD?' *"Daniel felt that "an academic setting" would offer him a better environment in which to explore the research questions he felt were necessary to address a health challenge that is particular to his ethnic community."* This aspect of trainee motivation for choosing a career in the biological sciences is not often considered or developed traditional basic research training programs. And with the low diversity of backgrounds among senior research laboratory mentors in the basic sciences, it is something that is poorly understood. With the push to translation of basic sciences in the cancer field, there is a real opportunity to keep the 'health challenge' present throughout the training and education continuum and to encourage more diverse applications of training in the basic and translational cancer research workspace.

**1C. Relevance of the Training and Education Program in CHDs.** With these significant barriers and the inadequate numbers and limited success of underrepresented minority investigators to diversify our cancer research workspace, we believe that knowledge gaps in population heterogeneity as Precision Oncology comes on line in cancer care facilities will serve to increase disparities among different groups of people and may further disenfranchise underserved and underrepresented groups in the delivery of cancer care in the U.S. Here, we propose an integrated cancer-related health disparities training and education program for consortium students, faculty and fellows designed to more fully integrate faculty, fellows and students from underrepresented and medically underserved communities in the research workforce with efforts to enhance awareness of health disparities in our research faculty and mentors who are jointly needed to identify, study and solve issues of C-HD. Success of our effort will be the creation and piloting of a unique training environment to address C-HD that will produce research excellence among a diverse faculty with a vision to translate impactful cancer breakthroughs to the community setting.

**2. Innovation.** The goal of this multi-institutional effort will be to develop an innovative training environment to enhance knowledge of C-HDs among established faculty mentors and to engage and empower, through knowledge and training, a cohort of exceptional cancer research scientists with an interest in conducting high-quality research aimed at addressing the biological causes of C-HDs. Research efforts in cancer biology are by definition aimed at understanding the causes of cancer with the goal of finding better ways to prevent, diagnose and treat. Given our current understanding of the extensive molecular heterogeneity of human cancers, training and education programs in basic and translational cancer biology must innovate to include the principles of population heterogeneity and its impact on the translatability of advances from the bench through the academic research hospital to the community practice. A significant unmet need in the field is attention to the biological underpinnings of C-HDs. As such, we believe that a solution to increase the overall quality of basic and translational scientific research into the biology of C-HDs, while addressing the lack of diversity in the cancer research workspace, is to join two challenges together through a training and education program in C-HDs aimed at training and educating both the mentor and the mentee. We envision creating a unique, cross-cultural conversation focused on population diversity, biology and C-HDs. Our expectation is that this unique training

and education environment we wish to pilot will serve 1) to better integrate our graduate students, fellows and early career faculty whose motivation comes from their community identity into the community and toward excellence in hypothesis driven research and 2) to enhance cultural competency and knowledge among exceptional cancer research mentors on the importance of population heterogeneity to basic and translational research of cancer biology and the importance of their mentorship in addressing C-HDs.

### **3. Strategy and Approach for Training and Education Program.**

**3A. Overview of Strategy.** The overarching strategy that we will pilot in this multi-institutional training and education program is to:

**3A.1 Develop a graduate level translational research Scholars in Biomedical Sciences (SBMS) training program with focus in cancer health disparities (C-HD).** This program will build upon an existing SUNY Stony Brook SBMS certificate program, which is designed to help graduate students obtain the skills to partner with clinicians and clinician scientists in the application of emerging biological knowledge to medical practice. Pilot project affiliated graduate students will propose a translational project, in our case addressing C-HD, and will be jointly mentored by a research mentor and a clinical co-mentor. Translational projects that represent collaborative projects between at least two of the three institutions (SUNY Stony Brook, SUNY Downstate and CSHL), and students from diverse backgrounds will be given high priority. We anticipate that the SBMS-CHD program will attract talented underrepresented minority students, who have personal interests in addressing cancer health disparities. By partnering clinical mentors with research mentors in this program, we also hope to catalyze the development of additional translational fusion projects addressing cancer-related health disparities.

**3A.2 Enhance awareness of cancer-related health disparities among established cancer research investigators.** During the course of this planning grant, we plan to host an annual symposium devoted to C-HDs at the Brooklyn Health Disparities Center. The Brooklyn Health Disparities Center is a collaboration of three partners: SUNY Downstate Medical Center (an academic medical center), the Arthur Ashe Institute for Urban Health (an established community based organization) and the Office of the Brooklyn Borough President (a government entity). SUNY Downstate Medical Center is the home of the Brooklyn Health Disparities Center. The Center's mission is to develop and implement models to reduce health disparities in minority and new immigrant populations in Brooklyn through basic, clinical, behavioral and community participatory research, community education and outreach and health professional training. At the annual symposium the consortium will bring together representatives of the community with SBMS-CHD trainees, their research and clinical mentors, the P20 staff, and interested clinicians and investigators from the three participating institutions.

**3A.3 Develop and evaluate new learning modules on C-HDs that will benefit existing cancer curricula.** An objective of the planning period will be to have our internal and external advisory board design new learning modules for C-HD that places emphasis on the role of the genetics, 'omics', biostatistics and bioinformatics as critical research tools for the study of biology as a cause of C-HDs that we can offer to the graduate programs at all the three participating institutions. A primary objective during the development phase will be creation of individual modules that will be piloted initially through traditional modalities of classroom education (didactic, facilitated, and symposia) with the intent to expand to include online training and education modules that can be adopted by other programs nationally. In this way, ALL trainees and many faculty will have a minimum knowledge on the importance of population diversity in cancer biology, oncology and cancer research. This simple modification to our educational platforms, while relatively modest to implement, has the potential to be truly transformative from a knowledge perspective and can be measured through recall tests to assess impact. In addition to developing these new learning modules, as part of planning, we will outline a strategy to test the modules and evaluate their effectiveness to enhance knowledge of how population heterogeneity influences the pathobiology of cancer and how this relates to differences in cancer incidence, tumor behavior and patient outcomes (See Section 5. Evaluation Plan).

**3B Approach.** In the planning period, we are requesting resources to complete Phase 1 of our SBMS-CHD initiative – Program Development and Implementation. We include a review of our history and rationale for the proposed partnership to address CHDs, our current status, and our timeframe for implementing the program.

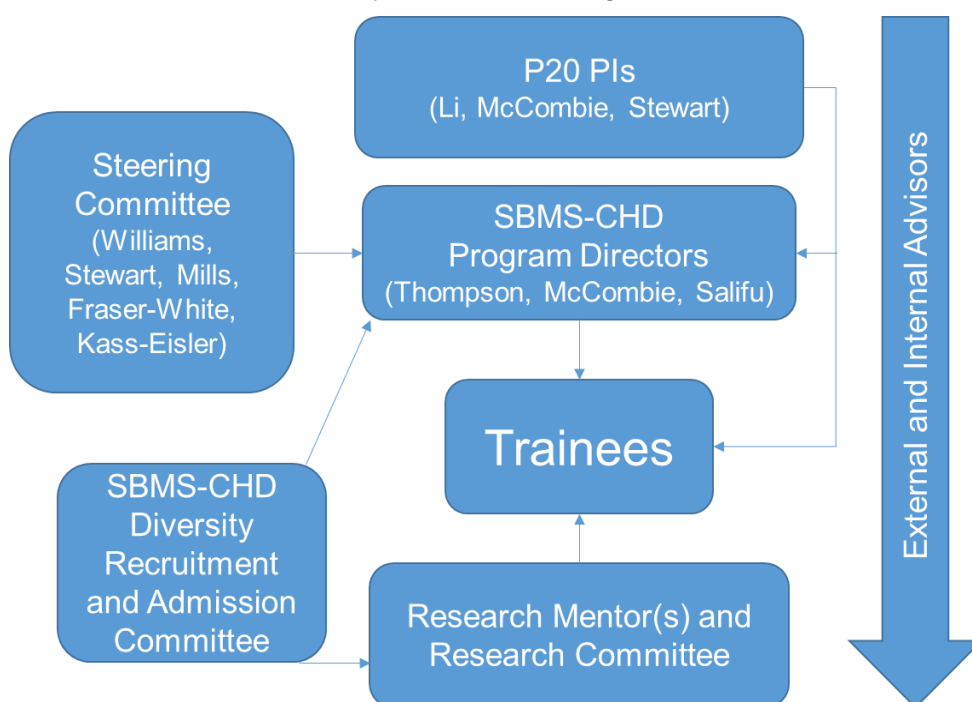
**3B.1 History and Statement of Need for a Scholars in BioMedicine in Cancer Health Disparities (SBMS-CHD).** As part of an ongoing effort to mentor and support RO1 funded investigator **Jennie Williams** and her interest in GI cancers and health disparities among AAs, senior research mentors from Stony Brook (Li), CSHL (McCombie) and Downstate (Salifu) initiated a collaboration for cancers of the GI tract that included a discussion on applying 'omic technologies towards characterizing the biological basis for the observed disparities in

incidence, presentation and outcomes of colorectal and pancreatic cancers occurring in AAs. This effort raised awareness of the presence of CHDs in the GI cancers, including CSHL investigators and served as a driving factor toward the creation of a tri-institution dialogue to focus on the biological basis of CHDs of the GI tract. This conversation is the impetus for the P20 planning application and is reflected in each component including the two pilot projects proposed and the training and education program.

**3B.2 Strategic Planning.** As part of a strategic planning process for programmatic development in C-HDs of GI cancer, to leverage our multi-institutional strengths toward C-HDs, training and education were identified. Creation of a SBMS-CHD was identified as a critical component for developing a comprehensive approach to address CHDs of the GI tract. The **following objectives** have been identified to accomplish this goal and are at different levels of progress.

**3B.2a Establish the Focus of the SBMS-CHD.** While the focus of our pilot projects are on C-HD in GI cancers, we believe that the SBMS-CHD awards should not be limited to translational projects in GI cancers but broadly to the biology of C-HD across cancer sites. Furthermore, we anticipate that the disciplines of Bioinformatics and Biostatistics will play an increasingly prominent role with the Behavioral and Social Sciences in C-HD research where biological determinants are integrated. As such, while we anticipate drawing initially from the biological departments, we hope to eventually draw from other disciplines to enhance cross discipline interaction and training. Further, because one of the aims of the SBMS-CHD is to increase diversity among the cancer research workforce, graduate students from diverse backgrounds will be prioritized.

**3B.2b Establish the Leadership Team for the Teaching and Education Program and the SBMS-CHD.** The joint Institutional (SUNY) and Cancer Center (CSHL) leadership of the Training and Education Program, will oversee the development of the SBMS-CHD and will work closely with the founding director, Dr. Stella Tsirkas, and founding clinical co-director, Dr. Vincent Yang, of the Stony Brook SBMS Program (see Biosketches, Letters of Support and <http://www.sbms.stonybrook.edu/>). The Teaching and Education Program leadership team has been tasked with aligning the SBMS-CHD with the SUNY Stony Brook SBMS Program and with existing graduate programs at their individual institutions. We strongly believe that development of the SBMS-CHD program will help the consortium attract top quality students from diverse backgrounds to the graduate programs at all three institutions, who may be interested in conducting CHD translational research. The leadership team includes the Key Personnel for the Institutional (SUNY) and Cancer Center (CSHL) Training and Education Program.



**Figure 2.** Organizational Structure of the SBMS-CHD Program.

**Patricia Thompson, Ph.D., contact PI, SUNY Stony Brook.** Dr. Thompson recently joined the faculty at Stony Brook University in the Department of Pathology as a Professor and as the Associate Director of Basic Science for the Stony Brook Cancer Center. She is the Institutional (SUNY) co-chair of this P20 Internal Advisory Committee. She has extensive experience successfully mentoring young investigators (undergraduate, pre and post-doctoral and early career faculty) and has taken a leadership role in multiple programs aimed at increasing diversity. She will take a leadership role in the development of the SBMS-CHD program and will work closely with Drs. Salifu, Stewart and McCombie in creating new learning modules on CHDs into the existing graduate programs at the three institutions.

**Moro O. Salifu, M.D. M.P.H., M.B.A. (co-PI, SUNY Downstate):** Dr. Salifu is Professor and Chair, Department of Medicine and Chief of Nephrology and Transplantation at SUNY Downstate Medical Center. He is co-Investigator on the Administrative Core. Dr. Salifu is also the contact PI on the current Brooklyn Health Disparities Center P20 and will take a leading role in organizing the annual Cancer Health Disparities Symposium which will be held at the Brooklyn Health Disparities Center.

**Mark Stewart, M.D.-Ph.D. (co-I, SUNY Downstate).** Dr. Stewart is the Dean of the School of Graduate Studies, Vice Dean for Research at SUNY Downstate. As Dean of the School of Graduate Studies he is directly involved in the selection of Ph.D. and M.D.-Ph.D. students at SUNY Downstate. He developed a mandatory grant writing class for the graduate programs at SUNY Downstate and is consequently well placed for planning the creation and introduction of new learning modules on CHDs into existing graduate studies curricula.

**W. Richard McCombie, Ph.D. contact-PI, CSHL.** Dr. McCombie is the Cancer Center (CSHL) contact PI for this P20 (See Administrative Core). Dr. McCombie, has been actively involved in teaching genomics both in the CSHL Watson School of Biological Sciences graduate program (<http://www.cshl.edu/gradschool>) and at SUNY Stony Brook, where he has joint appointments with both the SUNY Stony Brook Genetics graduate program (<http://www.stonybrook.edu/commcms/gradgenetics/people/faculty.html>) and the SUNY Stony Brook Biomedical Engineering graduate program ([http://bme.sunysb.edu/people/faculty/fac\\_program.html](http://bme.sunysb.edu/people/faculty/fac_program.html)).

He will work closely with Dr. Alyson Kass-Eisler who serves as the Curriculum Administrator for the Watson School of Biological Sciences as well as the Postdoctoral Program Officer for all CSHL postdoctoral fellows.

**3B.2c Establish a Training Education Program (TEP) Steering Committee.** The TEP members are distinct from the overall P20 internal advisory committee. The TEP members are charged with integrating the SBMS-CHD application and selection process with that of the existing SBMS program, recommending additional CHD learning modules, developing a strategic plan for recruitment of additional research and clinical co-mentors, obtaining additional institutional commitments for the SBMS-CHD, developing strategic plans for obtaining extramural funding for the SBMS-CHD, and defining the milestones and timelines and measures of success for achieving these goals.

**Jennie Williams, Ph.D. Chair, TEP Steering Committee.** Dr. Williams is the SUNY contact PI for pilot project P2, As Director of the SUNY Stony Brook Minority Access to Research Careers (MARC) program (see Overall Section she is well positioned to identify and recruit SUNY Stony Brook URM undergraduates to the SBMS-CHD and encouraging graduate students to participate in the P20 pilot projects or other translational research projects.

**Mark Stewart, M.D.-Ph.D., TEP Steering Committee Member.** Dr. Stewart is co-I on the Training and Education Program, a member of the leadership team for the SBMS-CHD (see above), and a member of the Internal Advisory Committee (see Overall and Administrative Core). See above.

**Alea Mills, Ph.D. TEP Steering Committee Member.** Dr. Alea Mills will serve as the CSHL co-chair. She is a faculty member of the Watson School for Biological Sciences and Director of the NCI T32 CSHL Cancer Gene Discovery and Cancer Biology Postdoctoral Research Training Grant and is thus well placed for advising on mentoring the SBMS-CHD trainees to prepare for post-graduate training.

**Alyson Kass-Eisler, Ph.D.** Alyson Kass-Eisler is the Trainee Coordinator at CSHL. She is the Curriculum Director of the Watson School of Biological Sciences and the Postdoctoral Program Officer for the Cold Spring Harbor Laboratory. Dr. Kass-Eisler will bring her considerable skills and experience to support and track the trainees who will be part of the education program for this project.

**Marilyn Fraser-White, M.D., TEP Steering Committee.** Dr. Marilyn Fraser-White is a member of this P20 External Advisory Board (see Administrative Core). Dr. Fraser White is Deputy Executive Director for the Arthur Ashe Institute for Urban Health (<http://www.arthurasheinstitute.org/arthurashe/about/>). The Arthur Ashe Institute sponsors a Health Science Academy Pipeline which exposes URM students, beginning in middle school (6-12), to the health sciences in order to increase minority representation in the healthcare and health sciences fields. Dr. Fraser-White has been engaged in development and implementation of health disparities learning modules for high school students and was recently a recipient of the SUNY Downstate President's Health Disparities Grant to develop a Health Disparities curriculum for Community Based Organizations in Brooklyn. Our plan is to further adapt these efforts to graduate students, post-doctoral trainees and faculty. Brooklyn Health Disparities Center also has a great training program called PRIDE Summer Institute, funded separately through NHLBI (<http://www.downstate.edu/pride/>). Our current organizational structure is shown in **Figure 2** (next page)

**3B.2c. Establish the Infrastructure for the SBMS-CHD.** The consortium plans to leverage the existing infrastructure from the SUNY Stony Brook SBMS program (<http://www.sbms.stonybrook.edu/program.html>) that was developed as a pilot program two years ago by founding director, Dr. Stella Tsurkis, Professor of Pharmacology, and Vice-Provost of Faculty Affairs, and clinical co-director, Dr. Vincent Yang, Professor and Chair of Medicine. This program is based on the concepts of the Howard Hughes Medical Institute Med into Grad (MIG) Initiative that was developed to address the growing gap between basic biology and medicine. The SBMS program facilitates the exposure of graduate students in Life Sciences programs to translational research in the medical and clinical sciences. The program currently has 10 trainees, however **none of the current translational projects address CHD and none of the current trainees are graduate students from diverse backgrounds**. We believe that by enhancing the Stony Brook SBMS program to an additional 4 slots reserved for our proposed tri-institutional SBMS-CHD, we will attract a greater number of potential students from diverse backgrounds interested in pursuing cancer-related health disparity research health from **all three** institutions. In preparing the revised P20 application, we have made significant progress toward our training and education infrastructure in the following areas:

**Identifying research mentors at the three institutions interested in participating in the SBMS-CHD program.** The research mentors interested in participating in the SBMS-CHD include the Key Personnel and members of the Internal Advisory Committee for this P20. In **addition, Table 1 below lists** additional research mentors with interest in participating in the SBMS-CHD program (see Biosketches and Letters of Support).

**Table 1.** Research Mentors for the SBMS-CHD program. Also see Biosketches and Letters of Support in Appendix)

	Title
<b>SUNY Stony Brook</b>	
Vincent Yang, M.D.-Ph.D	Professor, Chair, Department of Medicine
Yusuf Hannun, M.D.	Professor of Medicine, Director, SBCC
Lena Obeid, M.D.	Professor of Medicine, Vice-Dean of Research, Stony Brook Medicine
Jian Cao, Ph.D.	Professor of Medicine
Kenneth Shroyer, M.D.	Professor, Chair, Department of Pathology
R. Scott Powers, Ph.D.	Professor of Pathology, Director of Clinical Genomics, SBCC
Jing-fang Ju, Ph.D.	Associate Professor of Pathology, Director of Translational Research
Geoffrey Girnun, Ph.D.	Associate Professor of Pathology, Director of Metabolomics, SBCC
Michael Frohman, M.D.,Ph.D.	Professor, Chair of Pharmacology
Orlando Scharer, M.D.,Ph.D.	Professor of Pharmacology and Chemistry
<b>SUNY Downstate</b>	
M. Mahmood Hussain, Ph.D.	Professor of Cell Biology
Gladys Teitelman, Ph.D.	Professor of Cell Biology
Richard Kollmar, Ph.D.	Associate Professor of Cell Biology
Stacy Blain, Ph.D.	Assistant Professor of Cell Biology and Pediatrics, Director, Neoplasia Subunit
<b>CSHL</b>	
Darryl Pappin, Ph.D.	Associate Professor CSHL Cancer Center, Proteomics Shared Resource Head.
Linda VanAelst, Ph.D.	Professor and CSHL Cancer Center – Signal Transduction Program Director

**Identifying clinical co-mentors at SUNY Stony Brook and Downstate interested in participating in the SBMS-CHD.** The current Stony Brook SBMS program (<http://www.sbms.stonybrook.edu/program.html>) has an extensive list of clinical mentors including Key Personnel on this revised P20 application (e.g. Drs. Li, Bucobo, Denoya). Dr. Vignesh, co-I of pilot project **P2** as well as three additional SUNY Stony Brook clinicians directly

involved in the treatment of GI cancer patients have agreed to serve as a clinical co-mentors for the SBMS-CHD program (see Table 2).

**Table 2.** Additional Clinical co-Mentors for the SBMS-CHD program.

	Title
<b>SUNY Stony Brook</b>	
Minsig Choi, M.D.	Associate Professor of Medicine, Director of GI Oncology
Yue Zhang, M.D.	Assistant Professor of Medicine, GI Oncology
Samuel Ryu, M.D.	Professor and Chair of Radiation Oncology
Andrew Stessin, M.D.	Assistant Professor of Radiation Oncology
<b>SUNY Downstate</b>	
Shivakumar Vignesh, M.D.	Associate Professor of Medicine, Chief, Division of Gastroenterology and Hepatology
Evan Grossman, M.D.	Assistant Professor of Medicine, Division of Gastroenterology and Hepatology
Francesco Serafani, M.D.	Director of Surgical Oncology, King's County Hospital Center
Henry Talus, M.D.	Assistant Professor of Surgery
Gurinder Sidhu, M.D.	Division of Hematology and Oncology
Peter Han, M.D.	Department of Radiation Oncology

**Obtaining institutional commitment for funding the additional tri-institutional SBMS-CHD slots.** The consortium has secured a total of \$90,000 matching funds from SUNY Stony Brook and SUNY Downstate to fund 4 additional SBMS-CHD slots and to also cover graduate tuition, which is not currently supported by the Stony Brook SBMS program. The SBMS-CHD awards (\$15,000 for one year) will cover a 10% increase in the graduate students' stipend, the cost of supplies, equipment, and travel that the student will need to complete their translational project related to CHD.

**3B.2d Educating established research investigators on CHD.** In developing a robust SBMS-CHD program, one of the challenges will be to educate potential research mentors on CHD and to increase their cultural competency in mentoring URM trainees. One existing mechanism is the monthly GI Cancer Research meetings held at SUNY Stony Brook with video streaming to SUNY Downstate and CSHL. This can be expanded to encompass other organ sites as the program and interest increase. In this planning phase of developing a SBMS-CHD program, the TEP leadership, particularly Dr. Moro Salifu, will organize an annual symposium on Cancer Health Disparities that will include not only the SBMS-CHD participants (students, research mentors, clinical co-mentors, but community leaders and the larger research and clinical community from all three institutions. This symposium will model two previously held symposium on health disparities organized by Dr. Salifu. The structure of the symposium includes lunch and smaller workshops and breakout groups, allowing all the participants (trainees, faculty, clinicians and community leaders to continue their discussions in a more relaxed setting). All students and postdoctoral fellows will be required to submit a poster for presentation in an evening poster session. Faculty will be encouraged to have a poster representing their research groups and community members will be encouraged to attend the poster session. Importantly, this event will foster multidisciplinary research and collaborative cancer research efforts between basic scientists, clinicians at the three institutions and the communities. The CHD specific content for the symposium will be developed by a program committee that will be chaired by Dr. Salifu (Table 3 tentative topics/speakers for year 1).

**Table 3.** Tentative Topics and Speakers for First Annual Symposium in Cancer Health Disparities

Speaker	Affiliation	Topic
<i>Suggested Speakers- Keynote</i> Dr. Harold P. Freeman Dr. Otis Brawley (ACS) Dr. Sanya Springfield (NCI)		What do we mean by Cancer Related Health Disparity

Dr. John Carethers (keynote)	University of Michigan, Member EAB	Inflammation, colorectal cancer and race
Dr. Moro Salifu (keynote)	SUNY Downstate Medical Center	Community Engagement and Outreach are Critical to eradication of CHD
Dr. Patricia Thompson	SUNY Stony Brook	Reproductive Patterns, Breast Biology and Breast Cancer Patterns by Race/Ethnicity
Dr. Jennie Williams	SUNY Stony Brook	Micro RNAs and Colorectal Cancer
Dr. W. Richard McCombie	CSHL	Genetic background and cancer development and progression
Dr. David Tuveson	CSHL	Pancreatic cancer organoids and drug discovery – does donor race matter?
TBN	New York Genome Center	Sequencing, admixture and cancer discovery
Dr. Almeida Jonas	SUNY Stony Brook	TCGA – Who's There? Race representation in the TCGA
Dr. Elena Martinez	UC-San Diego	CHDs in the Hispanic Population – a role for geography
Drs. Amelie Ramirez or Melissa Simon	UT San Antonio or Northwestern University Feinberg School of Medicine	Diversifying Research and Clinical Trial Participation – The Cancer Disparities Research Network (CDRN)
Dr. Electra Paskett	College of Public Health, Ohio State University	Eliminating racial disparities in CRC in the real world (Community Practice Prevention)

### **Workshop/Breakout Topics that we would like to see evolve over time.**

**Cultural competency in the cancer research workplace for research mentors** - Workshop on population biology and CHD to increase awareness among our faculty mentors and generally, among our faculty about how population diversity influences the biology of cancer resulting in differences in incidence, treatment responsiveness, drug targets, tumor behavior and as a consequence patient outcomes.

**Increasing URM representation in research and clinical workforce.** Workshop for students, postdoctoral fellows and early career faculty to discuss strategies for succeeding in the research and clinical workforce. This is envisioned to be facilitated by senior URM faculty who have their own experiences and knowledge to guide the discussion.

**Community engagement in omics research and clinical trials.** Workshop for discussing the issues related to genomics research and need of diverse representation in sequencing and drug discovery activities. Would like to see this facilitated by a genomics researcher and a patient advocate, possible one with knowledge on ethical and legal issues raised in this domain for patient privacy protection.

**Population heterogeneity and drug development.** Workshop will focus on the role of race/ethnicity as a determinant of the distribution of a specific drug target in a given population. This workshop will include issues of sample size and robustness related to study design and statistical analysis. It is envisioned that this workshop group will be charged with developing one of the sessions for the second symposia.

**3B.2e The creation of new learning modules on CHDs into life science graduate curriculum.** We propose to develop short learning modules with the goal of increasing awareness among all graduate students about how population diversity influences the biology of cancer and that give rise to differences in incidence rates, treatment responsiveness, molecular targets, tumor behavior and as a consequence patient outcomes. We propose to develop these learning modules by adapting existing course content at each of the three institutions and “beta-test” these modules initially in the SBMS-CHD program, for eventual distribution to the mainstream graduate curriculum at the three institutions. Alternatively the SBMS-CHD program can provide participants with increased access to courses given at each of the three institutions.

### 3B.2e.i Existing courses/workshops amenable to piloting short CHD modules.

#### Cold Spring Harbor Laboratory (CSHL)

**Fundamentals of Cancer.** The primary objective of this biennial course is to ensure that trainees are provided with uniform baseline knowledge of cancer biology upon which they can build as they progress through and complete their training. The course is an intensive, off-site, three day didactic experience held at CSHL's Banbury Conference Center and encompasses topics that include oncogenesis, cell cycle, DNA replication, metastasis, angiogenesis, signal transduction, tumor microenvironment, as well as fundamental cancer diagnostic and therapeutic strategies.

**The Genome Access Course.** The Genome Access Course is an intensive two-day introduction to bioinformatics offered twice a year. The core of the course is the analysis of sequence information framed in the context of completed genome sequences. The course also features methods to assist the analysis and prioritization of gene lists from large scale microarray gene expression and proteomics experiments as well as methodologies for pathway analysis that facilitates a systems biology approach to cancer. This course is an excellent introduction to familiarize participants with current ways to access and interrogate informatics data. It provides a general overview of the multiple facets of data analysis, and instructs students on available approaches for accessing and interpreting various types of biological data they may be exposed to during their training.

**Advanced Sequencing Technologies and Applications.** This is a course that Co-PI McCombie is an instructor and that has been offered at Cold Spring Harbor for a number of years. The course focuses on both wet lab approaches and bioinformatics approaches to next-generation sequencing. A wide range of applications from genome sequencing to exome capture and the sequencing of samples from cancer are discussed in the course. The course also includes information on RNA sequencing and methylation detection by sequencing.

**Integrative Statistical Analysis of Genome Scale Data.** This two week course is designed to build competence in quantitative methods for the analysis of high-throughput molecular biology data. Detailed lectures and presentations by guest speakers is combined with hands on computer tutorials employing actual high-throughput data.

**Proteomics.** This intensive laboratory and lecture course lasts two weeks and focuses on cutting-edge proteomics approaches and technologies. Students are trained in several quantitative proteome analysis methods, gel analysis software, microcapillary liquid chromatography and mass spectrometry. The course provides students with the fundamental knowledge and hands-on experience necessary to perform and analyze proteomics experiments and to apply proteomics approaches to his/her research.

**Quantitative Imaging: From Cells to Molecules.** This course will focus on advanced quantitative fluorescence microscopy techniques used for imaging a range of biological specimens, from cells to single molecules. Students will gain a theoretical understanding of, and hands-on experience with, state-of-the-art techniques including wide-field fluorescence microscopy, laser scanning and spinning disk confocal microscopy, total internal fluorescence microscopy (TIRF), super-resolution methods (structured illumination, STED, STORM and PALM) and digital image processing and analysis.

**Single Cell Analysis.** The goal of this two week course is to familiarize students with the most recent cutting edge technologies for characterization of single cells. Important in this process will be highlighting the advantages to analysis of single cells in isolation and in their natural microenvironment.

**Mouse Development, Stem Cells & Cancer.** This lecture and lab course is designed for scientists interested in using mouse models to study mammalian development, stem cells and cancer. Lectures by leaders in the field provide the conceptual basis for contemporary research in embryogenesis, mathematical modeling of disease and development, organogenesis, embryonic, adult and induced pluripotent stem cells and cancer biology.

**Eukaryotic Gene Expression.** This course is designed for students, postdocs, and principal investigators who have recently ventured into the exciting area of gene regulation. The course will focus on state-of-the-art strategies and techniques employed in the field. Emphasis will be placed both on in vitro and in vivo protein-DNA interactions and on novel methodologies to study gene regulation.

**Grant Writing Workshops.** CSHL offers a professional 2-day grant writing and career development workshop each year that provides information about applying for and securing research and fellowship funding. The first day of the interactive grant writing program focuses on the grant application process, strategies to develop a strong and well-designed proposal and the roles and responsibilities associated with securing research funding. A unique feature of the workshop is the opportunity for participants to benefit from an insider's view on peer

review led by Senior CSHL Investigators who have served on public study sections. This portion of the program helps new investigators understand how best to prepare for the peer review process. The second day of the workshop is comprised of interactive writing sessions presented by internal and external professional science writers. Participants are encouraged to prepare in advance and to bring with them abstracts and papers they are working on to obtain one-on-one consultation during and after the workshop.

**Career Development Forum.** This weekend forum provides an opportunity for trainees to learn time and project management tactics as well as presentation and negotiation strategies that assist them in achieving and succeeding as new faculty. Participants will receive a reference book for researchers beginning an independent research laboratory entitled "At the Helm." This book contains excerpts from established investigators in which they face challenges typical to the new investigator, and serve as discussion material and future reference.

### **SUNY Stony Brook**

**Communicating Science: Improvisation for Scientists.** This course as well as the others listed below represent a series of graduate level courses offered by Stony Brook University's School of Journalism in spring 2015 in cooperation with the Alan Alda Center for Communicating Science. This innovative course uses improvisational theater techniques to help students communicate more directly and responsively. It's not about acting; it's about connecting with an audience.

**Communicating Science: Distilling your Message.** Students learn to speak clearly and vividly about their work and why it matters, in terms non-scientists can understand. Practice finding common ground with listeners and speaking different levels of complexity for different audiences. Includes a video interview with a journalist.

**Biology of Cancer.** A course on the biology of cancer with the emphasis on cancer as a disease of man. Lectures address human cancer as seen by the clinician and as basic research relates to human diseases. This course provides students with a link between courses in cell and molecular biology and the application of this basic information to tumor management.

**General Pathology.** Introduces the nature and causes of disease, death, reaction to injury, and repair. Analyzes associated structural changes in cells and tissues, with reference to their functional correlates.

**Colloquium in Molecular and Cellular Biology.** This is a weekly seminar type series where graduate students present their research interest.

**GRD 500 Human Subjects: Ethics and Responsible Conduct of Research.** This course is designed to introduce students to the major issues in the ethics of science and research. Using a combination of readings - written and web-based - videos, lectures, case discussion and other exercises, students will investigate the moral values intrinsic to science and the professional and social values with which scientists must comply. Each class will begin with an introductory lecture or video followed by discipline-based, small group discussions with the participation of faculty from the department or program from which the graduate students come.

**Advanced Principles of Pharmacology.** Advanced concepts of drug metabolism, pharmacokinetics, biochemical and molecular mechanisms of drug action and drug resistance in human disease states. Toxicological agents and environmental pollutants. The pharmacology of autotoxins, anti-inflammatories, immunosuppressants and anti-asthmatics. Rational drug design and drug receptor interactions using computer molecular modeling techniques. Includes discussion of specific cases taken from clinical practice and a presentation based on a set of selected readings.

### **SUNY Downstate and the Brooklyn Health Disparities Center (BHDC).**

Planning forward, a major resource is the Summer Institute Program to Increase Diversity Among Individuals Engaged in Health-Related Research (PRIDE) at BHDC. Dr. Salifu is the PI of the PRIDE program at BHDC, which provides an all-expense-paid research career advancement opportunity sponsored by the National Heart, Lung, and Blood Institute (NHLBI) through a variety of Summer Institutes including at SUNY Downstate. These exceptional mentored research programs address the difficulties experienced by junior investigators in establishing independent research programs and negotiating through the academic ranks. The primary outcome of this program is increased numbers of scientists and research-oriented faculty who are from ethnic groups currently under-represented in science and those with disabilities who successfully compete for external funding for scientific research in the biomedical and behavioral sciences in heart, lung, blood, and sleep (HLBS) disorders. Dr. Thompson also has experience with the NHLBI sponsored PRIDE program and having served as a mentor and member of the Washington University PRIDE program. With the collective experience of Drs. Thompson and Salifu with this outstanding training platform for early career scientists, we plan to adopt tools in place from the PRIDE and adapt them for our early career investigators as a C-HD PRIDE by initially integrating

two or three early career investigator from underrepresented communities into the existing PRIDE training domain with the intent to develop separately towards a 'PRIDE' for C-HD.

**Advanced Topics in Molecular and Cellular Biology.** The primary objective of this course is to expose students to advanced topics areas in complex human diseases that include application of new technologies such as proteomics and genomics, molecular genetics, advanced immunology, lipids and molecular mechanisms of diseases, translational cancer etc. This is offered every semester and generally includes a cancer topic area. We envision a direct application of a CHD module for a genomics, molecular genetics or translational cancer topic.

**4. Recruitment Strategies.** As presented in the Overall Research Strategy, both SUNY Stony Brook and SUNY Downstate have a substantial minority enrollment. SUNY Stony Brook was included in the 2013 Education Trust Report of higher education institutions that are leading in closing the minority college-completion gap. As such there is a significant institutional track record and commitment to addressing the educational and training needs of URM students. This includes experience in marketing our education and training programs to URM student populations across different academic institutions including Minority Serving Institutions. A major priority of the P20 TEP leadership team will be to work over the four years of the P20 award with each of the institutions to target intensive SBMS-CHD recruitment with the longer term goal of developing a relationship with these schools to establish a relationship with students earlier in the undergraduate education through summer training opportunities. Examples of target schools include Texas, Arizona, New Mexico and California schools with large Hispanic populations as well as the 20 top historically black college and universities and the 30 best U.S. colleges for minority students (e.g., University of San Francisco, Polytechnic Institute of New York University, University of Hawaii, Harvard, Rutgers, City University of New York). For those Universities in close proximity (Northeastern U.S.), the leadership plans to identify opportunities to be present on campuses in biology programs to highlight the program. For other more distant sites, we will create a YouTube video and a recruitment package for undergraduate programs.

**5. Program Evaluation.** Any effective education and training program requires a strategy for self- and independent evaluation. These are currently in the planning phase and will be formalized by the group during the planning period. As part of the planning phase, we will develop a robust set of qualitative metrics for measuring the success of the program. Table 5 highlights the key areas/activities where we will initially focus to obtain to evaluate program impact and success. Measurement strategies are indicated. Note, we are in the planning stage and do not wish to miss critical feedback and thus, will simultaneously develop evaluation tools that promote alternative forms of feedback. For this, we plan to develop a program evaluation committee to develop and review all evaluation tools and methods. We plan to engage both academic and non-academic partners/colleagues to promote innovation in how we evaluate the program and modify our evaluation tools as the program develops (See Table 5).

All three institutions have experience in tracking the career outcomes of former students and postdoctoral fellows. The TEP Leadership team will work closely with the SBMS Director and Clinical-Codirector (Drs. Tsirkas and Yang) to track the professional careers of the SBMS-CHD trainees after they graduate and receive their certificate for the SBMS-CHD program. The development of the SBMS-CHD alumni group will be very helpful for tracking as we invite alumni of the SBMS-CHD program to participate or possibly speak at the annual Cancer Health Disparities Symposium sponsored by the TEP. The TEP Leadership and the TEP Steering Committee will also be charged with establishing metrics for evaluation of the SBMS-CHD program.

**Table 5.** Examples of Qualitative Methods to Evaluate Program Impact and Effectiveness

Training Component	Area of evaluation	Methods of Assessment
Annual Symposium	Attendance	Number and professional and personal background of participants.
	Knowledge	Attendee response to short questionnaire on CHD topics covered during the conference using an Agreement Scale.
	Satisfaction	Attendee rated satisfaction with the symposium and topic areas. Each speaker and each session will be independently evaluated using a Performance Scale.

Training Component	Area of Evaluation	Methods of Assessment
CHD Modules	Knowledge	Short recall test on material presented in coursework based on an Agreement Scale.
	Satisfaction	Using a competence scale, students will be asked whether or not the short CHD modules were appropriate to the course objectives and whether or not they gained information that they had not previously known or had failed to consider.
Trainee Experience	Knowledge	Trainees will be asked a series of questions about their knowledge of CHDs. These will be questions that have a factual answer and will be scored for accuracy. The 'exam' questions will be based on information that they have been exposed to during the training period. These exam questions will be focused on materials for which the students are exposed during the newly developed coursework for the program.
	Satisfaction	Trainees will be asked several questions related to their experience that include the overall quality of the CHD training, whether or not it had an impact on their motivation to pursue a research career, whether or not it had an impact on the type of research they might want to do in the future etc. Initially we will use a developmental scale.
Mentor Experience	Knowledge	Mentors will be asked to evaluate whether or not they obtained new knowledge by participating in the program and whether or not this the knowledge of CHDs would change aspects of the research (experimental design, thinking about study relevance, hypothesis generation etc). We will also use a Competence Scale for the Mentors.  Mentors will also be asked if their experience with the mentees changed any of their attitudes about trainees from underserved/underrepresented communities and whether the experience would change any aspect of how they would mentor students in the future.
	Satisfaction	Mentors will be asked several questions related to their experience that will include the overall quality of the CHD training program, positive and negative attributes in terms of impacts on them or their mentees, and questions about whether or not they found the program overall beneficial (Performance/Competence based scale).

**6. Timeline for development of the SBMS-CHD program.** With our current progress toward the SBMS-CHD program based on an existing infrastructure and secured institutional funding for the four additional slots, we anticipate that we can launch the SBMS-CHD program early with awarding of the P20 funds. In fact, Dr. Martello-Rooney, co-Investigator of pilot project P2, has identified an underrepresented minority SUNY Downstate graduate student rotating in Dr. Martello-Rooney's laboratory that is interested in working on the pancreatic organoids for her Ph.D. thesis project. Consequently Dr. Martello-Rooney has budgeted for the graduate student's stipend in the revised Institutional (SUNY) P2 budget. Acceptance of this graduate student into the SBMS-CHD program would provide additional resources to this student (and her research mentors) for travel, equipment, supplies, courses, etc., as well as a 10% increase in her graduate stipend. We would anticipate because of the tri-institutional collaborative nature of pilot project 2, this graduate student would have the opportunity to rotate in the Dr. Tuveson's laboratory at CSHL to learn the method for growing pancreatic organoids from EUS-FNB biopsies. Timeline for the other activities include: development and small scale testing of 2-3 CHD modules in year 1 with additional modules launched in year 2 with implementation and evaluation in year 3 and 4. We will initiate the annual symposia in year 1 and continue throughout the funding period. Recruitment of fellows will follow for slots in years 2-4 with presentations to advisors by trainees beginning in year 2 and continuing at their annual visits in years 3 and 4. We anticipate early evaluation tools for year 1 with a full evaluation plan and implementation to include testing novel strategies of assessment in years 2-4. Project leaders will prepare and present an annual report to the PIs and SAB.

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**SUNY  
DOWNSTATE**  
Medical Center

University Hospital of Brooklyn  
College of Medicine  
School of Graduate Studies  
College of Nursing  
College of Health Related Professions  
School of Public Health

**Mark Stewart, M.D., Ph.D.**  
Dean, School of Graduate Studies  
and Vice Dean for Research

5 March, 2015

Ellen Li, MD, PhD  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine  
Stony Brook, New York 11794

Re: Collaborative Partners in Cancer Research

Dear Dr. Li,

I am pleased to join your team on the project entitled, "Partnership to Study Racial/Ethnic differences in GI cancer Biology." As Dean of the School of Graduate Studies and Vice Dean for Research at Downstate, I appreciate the significance of this project aimed at reducing health disparities in the context of gastrointestinal cancers, a major cause of mortality, frequently preventable with early detection, in all races. Your team comprised of faculty and researchers from Downstate, Stony Brook Medicine, and the Cold Spring Harbor Laboratories is outstanding.

In my roles as PI for the Training and Education core and member of the Internal Advisory Committee, I can offer considerable experience recruiting, mentoring, and ensuring the success of trainees at the undergraduate, graduate, and postgraduate levels. Downstate's School of Graduate Studies is our campus' focal point for community STEM education programs, research internships, educational pipelines, and many other kinds of research and educational activities that can be used by the Partnership. The personnel and facilities that you have brought together will serve as a fantastic training resource.

As the Director of the Research Core for Downstate's NIH-funded Health Disparities Center, I have access to the complete resources of our complementary projects, some of which may help with "best practices" and all of which will help with the innovative training pipeline from bench to bedside to community. As a co-lead on the SUNY-wide Health Network of Excellence, I can also say that your inter-institutional partnership is an outstanding example of how to bring the related research and training assets of our campuses together to have a major impact on healthcare.

In addition to the resources outlined above, the School of Graduate Studies will commit to supporting up to two students for each year of the project. This support consists of full-tuition waivers and a base stipend of \$27,477 plus fringe. This is a critical project for your patient community and ours, and will inform diagnostic, therapeutic, and access issues in significant ways. I look forward to our next steps.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark Stewart".

Mark Stewart, MD, PhD

**State University of New York Downstate Medical Center**

450 Clarkson Avenue, Box 41, Brooklyn, NY 11203-2098 • Phone 718 270-2740 Fax 718 270-3378

# **Stony Brook University Health Sciences Center**

*School of Medicine*

Department of Pathology

March 18, 2015

Dr. Ellen Li   
Chief, Division of Gastroenterology and Hepatology  
Stony Brook Medicine

RE: Feasibility studies to Build Collaborative Partners in Cancer Research

Dear Dr. Li

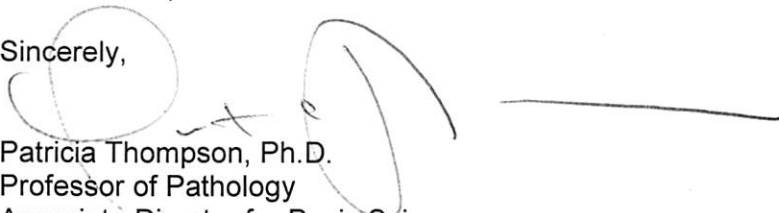
I am delighted to write this letter to confirm my willingness to serve as SUNY contact PI on the Training and Education Program and to co-chair the Internal Advisory Committee for the P20 planning grant application entitled "Partnership to study racial/ethnic differences in GI cancer biology" in response to PAR-14-152 "Feasibility studies to Build Collaborative Partners in Cancer Research".

As a result of my background coming from an underserved/unrepresented community in West Texas, I know the disparity that exists between cancer care in the underserved community and cancer care at the top academic cancer centers in the U.S. I also truly appreciate the array of challenges that students and early career investigators face when they come from underserved backgrounds and the need for a high bar and sustained motivation often based on wanting to make a difference. I am, thus highly committed to diversity in research sciences as I believe that education and empowerment of a few impact on the whole leading to advancement for all people.

My research focus in translating knowledge of breast and colorectal cancer biology to prevention of primary disease and metastasis in early stage patients. Over the past several years, I have focused my research efforts in the area of prevention with a special interest in applying strategies to study the impact of genetic susceptibility and tumor characteristics to prevention in high risk individuals. For colorectal cancer, my research focuses on identification of high risk preneoplastic lesions to better inform on the cost benefits of chemoprevention with non-steroidal anti-inflammatory agents, colonoscopy and age of initiation of screening and surveillance intervals.

I recently joined the faculty at Stony Brook University in the Department of Pathology as a Professor and as the Associate Director of Basic Science for the Stony Brook Cancer Center and will thus serve as a liason between the leadership of this P20 award and the administrative structure of the Stony Brook Cancer Center.

Sincerely,

  
Patricia Thompson, Ph.D.  
Professor of Pathology  
Associate Director for Basic Science  
Stony Brook Cancer Center

## Resource Sharing Plan: Training and Education

We will follow relevant NIH guidelines for data sharing. In accordance with NIH Resource Sharing Policy and the NIH Genomic Data Sharing Policy effective January 25, 2015, the investigators will share data and resources at the earliest opportunities throughout this research, subject to patient privacy concerns. Following careful curation of sequence data and clinical metadata, the Steering Committee will review the release of those data to the appropriate NCBI databases (dbGAP, Short Read Archive or SRA). Tables on cohort subject and sample metadata will be deposited in dbGAP, which is a controlled access database. We anticipate that the data generated by the team will be made available as somatic variant data and can therefore be placed on publicly accessible repositories. In addition, results will be written up and sent for publication in relevant journals and the investigators will seek to present publishable results at scientific conferences worldwide. All training modules with data obtained during evaluation will be made available for use by others at no cost.

December 4, 2015

Dr. Ellen Li  
Professor of Medicine  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook University School of Medicine  
101 Nicolls Road  
Stony Brook, NY

Award ID: 415604

Dear Dr. Li,

The Simons Foundation is pleased to notify you that your project, *The Stony Brook GI Biobank* (the "Project") has been approved for funding subject to the terms and conditions outlined in this letter.

The foundation agrees to pay to Stony Brook University \$750,000, including indirect costs, as follows:

\$250,000 for the period December 1, 2015 through November 30, 2016;  
\$250,000 for the period December 1, 2016 through November 30, 2017; and  
\$250,000 for the period December 1, 2017 through November 30, 2018.

Your first biannual payment will be disbursed on or before January 30, 2016.  
Payments will be disbursed biannually by the end of the first and third quarter.

In accepting the grant, you and your institution agree to be bound by the foundation's policies. Copies of these policies can be accessed online at <https://www.simonsfoundation.org/funding/policies-and-procedures/general>. You and your institution also agree to abide by all applicable laws and regulations, including those governing the conduct of research on humans or animals.

The foundation welcomes you into the collaborative community of Simons Investigators. As a member of that community you will be expected to share tools and renewable reagents developed with foundation funds and research results with others in the foundation community.

By accepting this grant, you and your institution are confirming that you or it are not aware of any requirements that would prohibit, delay or restrict your ability (or the ability of any parties with whom you are collaborating or affiliated on the Project) to share the

December 4, 2015  
Dr. Ellen Li  
Page two

research results from this Project. The foundation has no wish to participate in the commercialization of any intellectual property that may result from your grant.

Notwithstanding the above, you agree that the foundation has the right to release a summary of findings of the research within a reasonable period of time, certainly within six (6) months of the date of the grant expiration. Furthermore, the foundation may distribute information on our website, in press releases and/or other venues regarding the Project and may do so without seeking your permission.

Publications resulting from this project must carry the following acknowledgement: "This work was supported by a grant from the Simons Foundation (Award ID, Grantee)."

The foundation expressly reserves the right to suspend, reduce funding for or terminate the grant in support of this Project in the event the progress on the Project is substantially less than anticipated or overlapping funding is received for the Project. By accepting this grant you and your institution agree to notify the foundation immediately upon receiving notification of funding that may potentially overlap with your Simons grant.

The foundation requires that within 60 days following the end of each funding year that you submit a Renewal or Final Scientific Progress Report, unless you are requesting a Carry Forward or No-Cost Extension. If you are requesting a Carry Forward or No-Cost Extension, a Carry Forward Request or No-Cost Extension Request must be submitted 30 days prior to the end of the funding year.

Financial Statements are due within 60 days following the end of each funding year. Financial Statements are due 60 days following the end of each funding year even if you submit a Carry Forward or No-Cost Extension Request. Financial Statements can be accessed and completed online in the "Budget" section of proposalCENTRAL.

All web forms are available in the Deliverables section of proposalCENTRAL, <https://proposalcentral.altum.com/>.

Payments will be delayed if an investigator has not provided Financial Statements and/or Scientific Progress Reports within 60 days of the end of each funding year.

Investigators will be granted access to proposalCENTRAL, <https://proposalcentral.altum.com/>, a web-based tool, for submitting Scientific Progress Reports, Financial Statements and other documents to the foundation during the award period and must use such tool for submitting their reports and other documents.

December 4, 2015  
Dr. Ellen Li  
Page three

We expect that Simons Investigators will participate in conferences, workshops and symposia that the foundation organizes. All travel and accommodation expenses exclusively related to these meetings will be reimbursed outside of the award funds.

The first payment will be approved upon receipt of the Activation Agreement, which can be accessed and completed online in the "Deliverables" section of proposalCENTRAL, <https://proposalcentral.altum.com/>. The Activation Agreement will indicate that the attached revised budget and the terms as outlined in the policies document are acceptable to you and your institution. The policies document can be accessed online at <https://www.simonsfoundation.org/funding/policies-and-procedures/general>.

We appreciate your willingness to help ensure the success of this Project and we look forward to working with you in the months ahead. If you have questions about the administration of this Project, please contact Patricia Weisenfeld, Vice President, Special Initiatives, at 212-524-6082 or by email [pweisenfeld@simonsfoundation.org](mailto:pweisenfeld@simonsfoundation.org). Please reference the Simons Award ID, indicated above, in all correspondence with the foundation.

We greatly appreciate your efforts to advance our understanding of autism and related neurodevelopmental disorders and we welcome you to the community of Simons Foundation Investigators.

Sincerely, (

A handwritten signature in cursive script, appearing to read "Marilyn Simons".

Marilyn Simons  
President



**Grant Number:** 1P20CA192994-01A1  
**FAIN:** P20CA192994

**Principal Investigator(s):**  
ELLEN LI, MD

**Project Title:** 1/2: Partnership to study racial/ethnic differences in GI cancer biology

Ms. Adler, Andria  
Grant Administrator  
Stony Brook University  
W5510 Melville Library  
Stony Brook, NY 117943362

**Award e-mailed to:** OSP@stonybrook.edu

**Period Of Performance:**

**Budget Period:** 09/23/2015 – 08/31/2016

**Project Period:** 09/23/2015 – 08/31/2019

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of \$283,495 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to SUNY Research Foundation in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number P20CA192994. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website <http://grants.nih.gov/grants/policy/coi/> for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Tawana McKeither  
Grants Management Officer  
NATIONAL CANCER INSTITUTE

Additional information follows

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**SECTION I – AWARD DATA – 1P20CA192994-01A1****Award Calculation (U.S. Dollars)**

Salaries and Wages	\$62,713
Fringe Benefits	\$35,683
Supplies	\$2,805
Travel Costs	\$1,236
Other Costs	\$3,273
Consortium/Contractual Cost	\$116,473

Federal Direct Costs	\$222,183
Federal F&A Costs	\$61,312
Approved Budget	\$283,495
Total Amount of Federal Funds Obligated (Federal Share)	\$283,495
<b>TOTAL FEDERAL AWARD AMOUNT</b>	<b>\$283,495</b>

**AMOUNT OF THIS ACTION (FEDERAL SHARE)** \$283,495

SUMMARY TOTALS FOR ALL YEARS		
YR	THIS AWARD	CUMULATIVE TOTALS
1	\$283,495	\$283,495
2	\$289,027	\$289,027
3	\$288,919	\$288,919
4	\$288,919	\$288,919

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

**Fiscal Information:**

**CFDA Name:** Cancer Centers Support Grants  
**CFDA Number:** 93.397  
**EIN:** 1146013200F7  
**Document Number:** PCA192994A  
**PMS Account Type:** P (Subaccount)  
**Fiscal Year:** 2015

IC	CAN	2015	2016	2017	2018
CA	8475963	\$283,495	\$289,027	\$288,919	\$288,919

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

**NIH Administrative Data:**

**PCC:** 0FMB / **OC:** 414A / **Released:** MCKEITHET 09/18/2015  
**Award Processed:** 06/15/2015 11:31:44 PM

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**SECTION II – PAYMENT/HOTLINE INFORMATION – 1P20CA192994-01A1**

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at <http://grants.nih.gov/grants/policy/awardconditions.htm>

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**SECTION III – TERMS AND CONDITIONS – 1P20CA192994-01A1**

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

- The grant program legislation and program regulation cited in this Notice of Award.
- Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
- 45 CFR Part 75.
- National Policy Requirements and all other requirements described in the NIH Grants

- Policy Statement, including addenda in effect as of the beginning date of the budget period.
- e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
  - f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at <http://grants.nih.gov/grants/policy/awardconditions.htm> for certain references cited above.)

**Research and Development (R&D):** All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2. As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VI Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See <http://grants.nih.gov/grants/policy/awardconditions.htm> for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) P20CA192994. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see <http://grants.nih.gov/grants/policy/awardconditions.htm> for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: <http://publicaccess.nih.gov/>.

#### **Treatment of Program Income:** Additional Costs

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### **SECTION IV – CA Special Terms and Conditions – 1P20CA192994-01A1**

**INFORMATION:** In accordance with the National Cancer Institute's (NCI's) Fiscal Year (FY) 2015 funding policies, this award has been issued at 93.5% of the adjusted requested level\*. Support recommended for future years has been adjusted accordingly.

\*adjusted requested level: The requested level of support with adjustments made in accordance with the budget narrative in the summary statement and applicable grant policies.

\*Spreadsheets used to calculate this award are available upon request.

**INFORMATION:** Future year total cost commitments appearing on the award notice under "Recommended Future Year Total Cost Support" have been calculated by applying the negotiated facilities and administrative cost rate(s) in effect at the time of this FY2015 award to the committed total direct cost level for each future year.

**INFORMATION:** Although the budget period start date for this award is 9/23/2015, this award includes funds for twelve months of support. Future year budget periods will cycle on September 1. Allowable preaward costs may be charged to this award, in accordance with the conditions in the NIH Grants Policy Statement, (March 2015), and with institutional requirements for prior approval. A link to the NIH GPS is available through the following NIH Guide Notice: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-087.html>

**INFORMATION:** This award includes funds awarded for consortium activity. Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). A link to the NIH GPS is available through the following NIH Guide Notice: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-087.html>.

**INFORMATION:** See "Assurance Requirements and Institutional Review Boards" under Part II, Subpart A, Human Subjects, in the NIH Grants Policy Statement (NIHGPS)(rev. 3/2015), for specific requirements and grantee responsibilities related to the protection of human subjects, which are applicable to and are a term and condition of this award. A link to the NIH GPS is available through the following NIH Guide Notice: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-087.html>

This award reflects the National Cancer Institute's acceptance of the certification that all key personnel have completed education on the protection of human subjects, in accordance the NIH Grants Policy Statement (NIHGPS)(rev. 3/2015), "Education in the Protection of Human Research Subjects." A link to the NIH GPS is available through the following NIH Guide Notice: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-087.html>

Any individual involved in the design and conduct of the study that is not included in the certification must satisfy this requirement prior to participating in the project. Failure to comply can result in the suspension and/or termination of this award, withholding of support of the continuation award, audit disallowances, and/or other appropriate action.

**INFORMATION:** This award, including the budget and the budget period, has been discussed between Renee Carruthers of the National Cancer Institute and the Grantee on 9/18/15.

## STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

**Grants Management Specialist:** Renee Carruthers  
**Email:** carruthersr@mail.nih.gov **Phone:** 301-631-3018 **Fax:** 301-451-5391

**Program Official:** Behrouz Davani  
**Email:** behrouz.davani@nih.gov **Phone:** 240-276-6098 **Fax:** 240-276-7862

## SPREADSHEET SUMMARY

**GRANT NUMBER:** 1P20CA192994-01A1

**INSTITUTION:** SUNY Research Foundation

Budget	Year 1	Year 2	Year 3	Year 4
Salaries and Wages	\$62,713	\$62,713	\$62,713	\$62,713
Fringe Benefits	\$35,683	\$35,683	\$35,683	\$35,683

Supplies	\$2,805	\$2,805	\$2,805	\$2,805
Travel Costs	\$1,236	\$1,098	\$1,030	\$1,030
Other Costs	\$3,273	\$3,273	\$3,273	\$3,273
Consortium/Contractual Cost	\$116,473	\$122,223	\$122,223	\$122,223
TOTAL FEDERAL DC	\$222,183	\$227,795	\$227,727	\$227,727
TOTAL FEDERAL F&A	\$61,312	\$61,232	\$61,192	\$61,192
TOTAL COST	\$283,495	\$289,027	\$288,919	\$288,919

Facilities and Administrative Costs	Year 1	Year 2	Year 3	Year 4
F&A Cost Rate 1	58%	58%	58%	58%
F&A Cost Base 1	\$105,710	\$105,572	\$105,504	\$105,504
F&A Costs 1	\$61,312	\$61,232	\$61,192	\$61,192

## COVER PAGE

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### **TARGETED RESEARCH OPPORTUNITIES 2016/2017**

**APPLICATION FOR PILOT / FEASIBILITY STUDY**

Received:  
Sent to reviewers:  
Review Board meeting:  
Applicant notified:

**Category:** (indicate from list on 2016/2017 RFA)  
Fusion

**Title:** (not to exceed 56 characters)

**Diabetes, glycemic control & progression to colon cancer**

**Principal Investigator:**

Joshua D. Miller, MD, MPH

**Department:**

Medicine - Endocrinology and Metabolism

**Co-Investigators and Departments:**

Ellen Li, MD, PhD  
Jonathan Buscaglia, MD  
Igor Kravets, MD, Endocrinology and Metabolism  
Juan Carlos Bucobo, MD, Gastroenterology and Hepatology  
Chris Lascarides, MD, Gastroenterology and Hepatology  
Eduardo Quintero, MD, Gastroenterology and Hepatology  
Crystal Antoine, MD, Medicine  
Li Huang, MD, Medicine  
Lorenzo Ottaviano, MD, Medicine  
Asem Qadeer, MD, Medicine  
Bushra Wazed, MD, Medicine  
Adam Solis-Cohen, MD, Medicine  
Wendy Podany, MD, Medicine  
Mohammad Khan, MBBS, Medicine  
Shaha Nabeel, MBBS, Medicine  
Matthew Murray, MS, Medicine  
Brandon Lung, Stony Brook University School of Medicine  
Jose Deniz, Stony Brook University

**This signature certifies that you are in support of this application and departmental funds match if required.**

**Signature of Department Chair:**

**Signature of Department Administrator:**

**Summary:** *(Not to exceed 150 words or the space below)*

The proposed study seeks to analyze the effects of glycemic control and insulin resistance on the progression of colorectal cancer along the adenoma-carcinoma pathway in patients with diabetes mellitus. Population studies have long established an increased risk for colorectal cancer in patients with diabetes. However, there is limited evidence outlining the cause. This study will look both retrospectively and prospectively at patients who present for screening colonoscopy. Patients with diabetes will be categorized by glycemic control (based on hemoglobin A1c “HbA1c”) and examined for rates of adenoma prevalence and pathology. Understanding the progression of the adenoma-carcinoma pathway, and where diabetes mellitus may play a role, is crucial in determining the effect the disease has on the development of colorectal cancer, and may lead to novel and unique treatments and therapies for cancer patients with diabetes.

*See the 2016/2017 TRO RFA for support periods and funding amounts.  
(Instructions on the following page)*

**2016/2017 TRO Instruction Checklist**

**I) Completion of the 2016/2017 Targeted Research Opportunities Award Survey:**

<https://www.surveymonkey.com/r/3J3NFCP>

*If you have previously completed the survey please proceed to completion of the (II) cover page.*

**II) Cover Page** *\*\*Applications will not be considered without the Department Administrator and Chair’s signature on the front of the cover page\*\**

**III) Narrative:** Total, no more than 5 pages. Please include the following information:

- a) Rationale and Background
- b) Specific Aims
- c) Experimental Design & Preliminary Data
- d) Significance
- e) Relevance to Targeted Area
- f) Forms, Figures, and Tables (to be included in the 5 page limit)
- g) Citations (to be included in 5 page limit)
- h) Font size 11pt

*This is an all inclusive requirement. The application narrative (a-h) cannot exceed the 5 pages.*

**IV) Budget Outline & Justification:** 1 page budget, 1 page justification.

*(Indirect/administrative costs, travel, conference fees, memberships, subscriptions and PI and Co-PI salary support is prohibited) Except for Clinical Research Awards.*

**V) NIH- Biosketch and Other Support:**

*(PHS 398 modular 4-page format only)*

**VI) Applications are to be submitted as a single PDF file.** *Please review and follow the instructions on the application guide document.*

**VII) Follow the TRO application guide to submit your proposal**

***N.B.: No appendices will be accepted.***

*Failure to comply with the above will result in application being returned without benefit of review.*

*Applications do not require prior approval by the Office of Sponsored Programs. Please submit application package electronically and follow the instructions from the TRO application guide when submitting your proposal. Note that this website will not accept applications after 5:00 p.m. on May 13, 2016.*

*All reports and sponsor action requests will be submitted via TRO Central for consideration. Awarded applicants will be assigned TRO central login credentials at the time of grant activation.*

**See supplemental for Fusion Award.**

**See supplemental for Clinical Research Award.**

*\* The OVPR reserves the right to request a COID for funded awards.*

## **Hypothesis and Specific Aims**

Diabetes mellitus has been shown to be a risk factor for colorectal cancer<sup>1-4</sup>. The prevalence of diabetes is increasing, and thus the number of individuals at risk for colorectal cancer is also rising<sup>5</sup>. Colorectal cancer largely develops through the adenoma-carcinoma pathway in which normal epithelium becomes an adenomatous polyp, an advanced adenomatous polyp, and finally develops into an invasive carcinoma. While the literature has clearly shown a connection between diabetes and colorectal cancer, no consensus has been reached about the impact of diabetes on colorectal adenoma development, with multiple reports of conflicting findings<sup>6-11</sup>. We are interested in examining where in the adenoma-carcinoma pathway diabetes may play a role by examining the influence of diabetes on the risk of developing both early and advanced colorectal adenomas. In order to do this, we will phenotype patients with diabetes who present for screening colonoscopy as either having poorly controlled or well-controlled diabetes, based on their glycemic control. Glycemic control in patients with diabetes is affected by many variables including degree of insulin resistance, residual pancreatic secretory function, and hepatic gluconeogenesis, among others. We will assess these variables in patients undergoing screening colonoscopy by examining several factors including, fasting plasma glucose (FPG), HbA1c, homeostatic model assessment of insulin resistance and  $\beta$ -cell function (HOMA-IR/HOMA- $\beta$ ), and current medication regimen. In addition, we will further sub-classify any adenomas found during colonoscopy as either early or advanced ( $>1$ cm, villous features, or high grade dysplasia). By phenotyping with respect to disease control and adenoma type, we will be able to assess what effect diabetes, hyperglycemia, and hyperinsulinemia have on the development of these lesions, and what point in the adenoma-carcinoma pathway is impacted most by the disease. We hypothesize that poor glycemic control increases the risk of developing adenomas and advanced adenomas, eventually leading to malignancy through the adenoma-carcinoma pathway. We plan to test this hypothesis using both a retrospective and prospective design in the following specific aims:

**Aim 1:** We will retrospectively study patients who received screening colonoscopies at SBUH from 1/1/2010 - 9/30/2015. In our retrospective analysis, we plan to collect additional clinical covariates related to diabetes including measures of glycemic control such as point of care fasting plasma glucose and HbA1c values, as well as the patient's current medication regimen. We will categorize patients with diabetes as poorly controlled and well-controlled based on these measurements and the medications taken. In order to address the effect poor glycemic control has on the progression of the adenoma-carcinoma sequence, we also plan to expand our collection of clinical metadata to include more information about the pathology of adenomas found in these patients. With this dataset we can then compare the effects of having well or poorly controlled diabetes on the development of adenomas and advanced adenomas to the adenoma detection rate in patients without diabetes.

**Aim 2:** We will expand our prospective GI Biobank recruitment, with specific attention to diabetes-related covariates, to include all patients with diabetes undergoing initial screening colonoscopies. These patients will be asked to donate blood samples, access to formalin fixed paraffin embedded (FFPE) samples archived by the Pathology Department, and longitudinal clinical information. Research blood samples will be used to perform preliminary laboratory tests to generate data on hyperglycemia and hyperinsulinemia (FPG, HbA1c, HOMA-IR/HOMA- $\beta$ ). The clinical information we collect from these patients will have a particular focus on diabetes-related covariates such as diabetes medications. These data will be used to extensively phenotype patients with diabetes presenting for screening colonoscopy as either well-controlled or poorly controlled. We will then assess the impact glycemic control has on adenoma development by comparing the adenoma detection rate in these patients. Over 2 years, we hope to prospectively recruit approximately 700 subjects for this research.

## **Background and Clinical Significance**

The Stony Brook GI Biobank operates as an organ specific module under the Stony Brook Medicine Biobank, directed by Dr. Shroyer, and thus operates under the institutional NYS Biobank License issued for Stony Brook University. Since its inception, tissue, blood and stool samples have been collected from over 900 subjects and have been linked to detailed longitudinal clinical metadata. The GI Biobank collects samples and clinical data in a project-directed manner, involving the clinicians caring for patients with GI disorders in the design and execution of clinical translational projects. Through this interdepartmental collaboration, we can identify and obtain the consent of potential subjects scheduled for surgery or endoscopic procedures at SBUH and ensure that members of the GI Biobank staff are present to collect and properly preserve the samples. In addition to donation of research samples, the consent for the GI Biobank grants permission to access archived FFPE tissue samples from the Department of Pathology for genomic studies and also grants permission to collect longitudinal clinical metadata over the patient's lifetime. Rigorous curation of the clinical metadata is critical for interpreting data generated from patient samples. Thus far, the clinical metadata has included data on age, gender, smoking, diabetes, obesity, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), personal and family history of colonic neoplasia, as well as medical insurance status, which is a measure of access to health care<sup>12</sup>. The clinical

data elements collected by the GI Biobank on potential covariates are not currently available on nationally maintained databases as they do not include information on diabetes mellitus, obesity, smoking etc. Therefore, building and maintaining large databases such as the GI Biobank represent a necessary and vital component of conducting meaningful research in areas such as colorectal cancer treatment and prevention.

Diabetes mellitus, particularly type 2, has been associated with an increased risk (OR: 1.3 – 1.4) of colorectal cancer in multiple studies<sup>1-4</sup>. While this phenomenon is well documented in the literature, the underlying reasons by which diabetes increases the risk for developing colorectal cancers remains unclear. Understanding the impact of diabetes on cancer development is further complicated by conflicting evidence as to whether there is an increased prevalence of adenomas among patients with diabetes mellitus compared to those without<sup>6-11</sup>. This observation leads us to question where in the adenoma-carcinoma pathway diabetes could have an impact, accelerating the development of colorectal cancer. To properly understand the risk conferred by diabetes, we will examine diabetes-related variables such as HbA1c, FPG, and HOMA-IR/HOMA- $\beta$ . These variables will help to clarify the potential association between glycemic control, insulin resistance and pancreatic  $\beta$ -cell function in diabetes patients at risk for colon cancer. Additionally, diabetes medications, particularly metformin and insulin, can have a significant impact on the development of adenomas and adenocarcinomas. Insulin has been associated with an increased risk of colonic neoplasia (adenoma and carcinoma) whereas metformin, which does not act by increasing insulin secretion, is associated with a reduced risk<sup>13-18</sup>.

Understanding how diabetes affects the adenoma-carcinoma pathway and potentially increases the risk of adenocarcinoma development will significantly impact the clinical management of patients with diabetes. This study's exploration of the impact of medications on the development of adenomas or adenocarcinomas could impact clinician choice in medication management of people with diabetes, especially those deemed high risk for colonic carcinoma. Data outlining the relationship between hyperinsulinemia and hyperglycemia (as related to HbA1c, plasma glucose, and HOMA-IR), could provide more robust support for patients adopting lifestyle modifications to lower their risk of developing cancer. Additionally, this study can better inform clinical practice recommendations/screening guidelines for preventing colorectal cancer and detecting early adenomatous lesions. Finally, by generating a robust database of linked clinical information and metabolic profile of patients with diabetes, this study will allow for future investigation into diabetes-specific covariables in endoscopy and progression of colorectal cancer.

### **Preliminary Evidence/Feasibility**

In order to understand the impact of diabetes on the development of colonic adenocarcinoma in the Stony Brook Medicine patient population, we reviewed data from 410 patients in the GI Biobank who underwent surgical resection at Stony Brook between 2010 and 2015. One hundred and sixty six out of the 410 surgical patients underwent surgery as treatment for colorectal cancer, while the remaining 234 patients underwent surgery for non-cancer indications. Of the 166 colorectal cancer patients we examined, one fourth of the subjects (40/166) had diabetes, whereas only one tenth of the 234 non-cancer patients (24/234) had diabetes (Figure 1A). These results support the observation that diabetes is indeed associated with colorectal cancer ( $p = 0.0003$ ; OR: 2.778).

Similarly, to estimate the impact of diabetes on the development of colonic adenomas in the Stony Brook Medicine patient populations, we reviewed data from the Project SCOPE study which retrospectively analyzed screening colonoscopy records at Stony Brook to understand the completion rate of screening colonoscopies among minority populations<sup>12</sup>. Project SCOPE data contained information on diabetes status and the presence of adenomas during colonoscopy. Analysis of these data did not show any association ( $p = 0.53$ ) between diabetes mellitus and adenoma development (Figure 1B). Adenomas were not differentiated between early (size  $\leq 1$  cm, no villous features or low grade dysplasia) and advanced adenomas (size  $\geq 1$  cm, villous features, or high grade dysplasia) so we were not able to address whether diabetes mellitus was associated with advanced adenomas. Glycemic control was not assessed in the Project SCOPE study as a specific contributor to advanced adenoma risk, nor was the effect of diabetes medications explored, which could serve as potential confounders in the analysis.

### **Experimental Design and Methods**

**Aim 1:** To achieve Aim 1, we will retrospectively study patients who underwent screening colonoscopies between 1/1/2010 and 9/30/2015 at Stony Brook Medicine. We have identified 7,000 such cases within this timeframe. In order to test the hypothesis that hyperglycemia associated with poorly controlled diabetes will be positively correlated with the presence of advanced adenomas in patients undergoing screening colonoscopies, we will need to extensively phenotype patients with diabetes mellitus by reviewing FBG, HbA1c, and antidiabetic drug regimens in patients with diabetes presenting for screening colonoscopy. Finally, to address where diabetes mellitus impacts the adenoma-carcinoma sequence, we will also collect detailed information on adenoma pathology in order to phenotype adenomas as

early or advanced (Table 1). From our retrospective analysis, we hope to demonstrate an association between poor glycemic control and the development of advanced adenomas.

**Power Analysis, Aim 1:** We performed a power analysis in order to understand what the detectable effects will be for diabetes and glycemic control in the retrospective analysis. To perform the analysis we made several assumptions:

1. Out of the 7,000 screening colonoscopy patients in the retrospective analysis, we estimate 13% will carry a diagnosis of diabetes<sup>12</sup>.
2. Based on previous reports, we estimate an adenoma detection rate of 25%<sup>12</sup>.
3. Based on previous reports, we estimate that approximately 40% of subjects with diabetes undergoing colonoscopy will have an HbA1c > 7.5, categorized as “poorly controlled diabetes”<sup>19, 20</sup>.

The minimum effect to reach 80% power ( $\alpha = 0.05$ ) was computed analytically and validated by 1000 simulations. All subjects with diabetes were assumed to have equal probabilities of presenting with either an adenoma or an advanced adenoma. A logistic model was built:

$$lo(adenomai) = \beta_0 + \beta_1 diabetes_i$$

Index (i) denotes the patient in the model. *diabetes* is an indicator variable, which is given a value of 1 if the  $i^{th}$  patient has diabetes, or 0 if the patient does not have diabetes. The inclusion of *diabetes* in this model was informed by the Wald’s test. We estimate that at least 256 diabetic patients with adenomas need to be identified to confirm our hypothesis that there is a significant difference of proportions of adenoma between diabetic vs. non-diabetic patients. Accordingly, the minimum population adenoma detection rate among diabetic patients is 29.35% (assuming an adenoma detection rate of 25% among non-diabetics). For advanced adenomas, a minimum detection rate of 4.13% must be observed among subjects with diabetes to achieve 80% power.

Poor diabetes control, defined as having an HbA1c > 7.5%, will also be included in the logistic model:

$$lo(adenomai) = \beta_0 + \beta_1 diabetes_i + \beta_2 Poorcontrol_i$$

*Poorcontrol* is an indicator variable, which is given a value of 1 if the  $i^{th}$  subject has poor diabetes control or 0 if the subject does not have poor diabetes control. Assuming that diabetics with good control have detection rates of adenomas and advanced adenomas of 29.35% and 4.13%, respectively, we estimate that among subjects with poor glycemic control, a minimum population detection rate of 37.7% for adenomas and 8.5% for advanced adenomas must be observed to achieve 80% power.

**Aim 2:** To achieve Aim 2, we will expand our prospective GI Biobank recruitment to patients with diabetes undergoing initial screening colonoscopies for donation of research specimens and clinical information. Although it is recommended that patients with diabetes should routinely be monitored with respect to their HgbA1c levels<sup>21</sup>, it is clear from our preliminary retrospective review that physician adherence to this recommendation and/or recording of this information in electronic medical records is not uniform. For this reason, the GI Biobank proposes to initiate prospective recruitment of all patients with diabetes undergoing initial screening colonoscopy to donate blood, access to FFPE samples archived in the Pathology Department, and longitudinal clinical information. The blood samples and clinical information will be used to generate data on hyperglycemia and hyperinsulinemia and insulin resistance (Table 2). Funds obtained from the Fusion Seed Grant Award will be used to generate preliminary laboratory results from 700 patients undergoing screening colonoscopy. Our overall adenoma detection rate is approximately 25% from the Project SCOPE study and is in agreement with standards for adenoma detection rate<sup>22</sup>. We hypothesize a similar rate of detection in diabetes patients with good glycemic control (i.e. HbA1c ≤ 7.5%). Over two years, we hope to prospectively recruit 700 subjects with diabetes to ascertain the adenoma detection rate in patients with poor glycemic control as compared to those with good glycemic control and the non-diabetic population.

**Power Analysis, Aim 2:** We performed a power analysis in order to understand what the detectable effects will be for diabetes and glycemic control based on the hypotheses that both the adenoma and advanced adenoma detection rate will be significantly higher in subjects with poorly controlled diabetes (HbA1c > 7.5) compared to those with good glycemic control (HbA1c ≤ 7.5) and significantly higher than that reported in subjects without diabetes. In order to perform the analysis, we made several assumptions:

1. Based on previous reports, we estimate that approximately 40% of subjects with diabetes undergoing colonoscopy will have an HbA1c > 7.5, categorized as “poorly controlled diabetes”<sup>19, 20</sup>.
2. We estimate subjects with HbA1c ≤ 7.5% will have an adenoma detection similar to the non-diabetic population of 25%<sup>12</sup>.

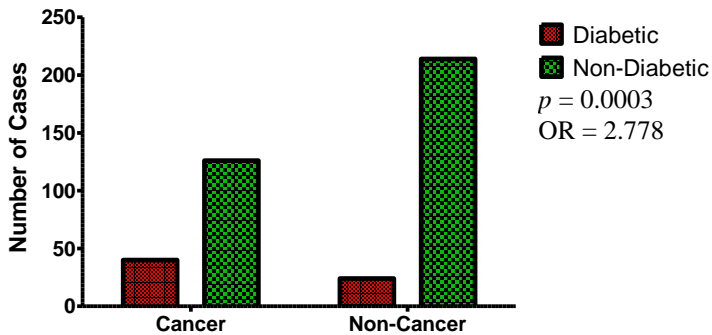
In order to achieve 80% power ( $\alpha = 0.05$ ), at least 98 subjects with poor glycemic control (35%) must present with adenoma.

## Clinical Adoption Strategy

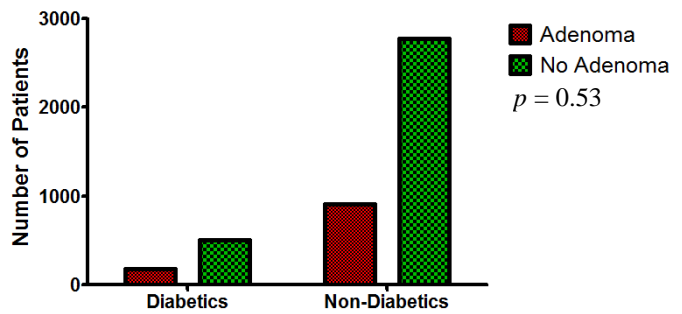
Should our hypothesis prove true, the implications for clinical care and secondary prevention in patients with diabetes will be far-reaching. Prevention of micro- and macro-vascular complications of diabetes forms the foundation for anticipatory guidance offered to patients with the disease. Knowledge of the impact of hyperglycemia on cancer risk would prove pivotal in further encouraging diabetes self-management and attention to glycemic control. Moreover, this could serve as a means to encourage greater utilization of screening colonoscopy in patients with diabetes.

## Forms, Figures & Table

**A Univariate Analysis of Tissue Bank Patients Analyzing Diabetic Risk for Colon Cancer**



**B Univariate Analysis of Project SCOPE Data for Adenoma Presence vs. Diabetes status**



**Figure 1.** (A) Prevalence of diabetes in colorectal surgery cases of both cancer and non-cancer patients in the Stony Brook GI Biobank. The p-value and odds ratio were obtained from a Fisher's exact test. (B) Prevalence of diabetes and adenomas in colonoscopy patients from the project scope study. The p-value was obtained from Chi-Square test.

Diabetes Mellitus Status	Diabetes medications at the time of colonoscopy
<ul style="list-style-type: none"> <li>Type 1</li> <li>Type 2</li> </ul>	<ul style="list-style-type: none"> <li>Insulin (subcutaneous human, subcutaneous animal, concentration U100, U300, U500)</li> </ul>
Hyperglycemia data	
<ul style="list-style-type: none"> <li>Fasting plasma glucose (point of care day of colonoscopy)</li> <li>Hemoglobin A1c (most recent available value pre-colonoscopy)</li> </ul>	<ul style="list-style-type: none"> <li>Insulin-pump status</li> <li>Sulfonylureas</li> <li>Meglitinides</li> <li>Metformin</li> <li>Thiazolidinediones</li> <li>Incretin based therapies (Dipeptidyl peptidase-4 inhibitors and GLP-1 receptor agonists)</li> </ul>
Adenoma pathology	
<ul style="list-style-type: none"> <li>Size</li> <li>Histopathology</li> <li>Presence of dysplasia</li> <li>Location</li> <li>Number of Adenomas</li> </ul>	<ul style="list-style-type: none"> <li>SGLT-2 inhibitors</li> <li>Acarbose</li> </ul>

**Table 1** – List of factors and characteristics that will be collected during the retrospective analysis and used to phenotype subjects with diabetes as poorly controlled or well controlled and adenomas as early or advanced.

Diabetes Mellitus Status	Diabetes medications at the time of colonoscopy
<ul style="list-style-type: none"> <li>Type 1</li> <li>Type 2</li> </ul>	<ul style="list-style-type: none"> <li>Insulin (subcutaneous human, subcutaneous animal, concentration U100, U300, U500)</li> </ul>
Hyperglycemia data (venous blood sample on day of colonoscopy)	
<ul style="list-style-type: none"> <li>Fasting plasma glucose *</li> <li>Hemoglobin A1c</li> <li>Insulin level *</li> </ul>	<ul style="list-style-type: none"> <li>Insulin-pump status</li> <li>Sulfonylureas</li> <li>Meglitinides</li> <li>Metformin</li> <li>Thiazolidinediones</li> <li>Incretin based therapies (Dipeptidyl peptidase-4 inhibitors and GLP-1 receptor agonists)</li> </ul>
Adenoma pathology	
<ul style="list-style-type: none"> <li>Size</li> <li>Histopathology</li> <li>Presence of dysplasia</li> <li>Location</li> <li>Number of Adenomas</li> </ul>	<ul style="list-style-type: none"> <li>SGLT-2 inhibitors</li> <li>Acarbose</li> </ul>

**Table 2** – List of factors and characteristics that will be collected during the prospective analysis and used to phenotype subjects with diabetes as poorly controlled or well controlled and adenomas as early or advanced. (\*to calculate HOMA-IR/HOMA- $\beta$ )

## **References**

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4. Yuhara H, Steinmaus C, Cohen SE, et al. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? *Am J Gastroenterol* 2011;106:1911-21; quiz 1922.
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7. Dash C, Palmer JR, Boggs DA, et al. Type 2 Diabetes and the Risk of Colorectal Adenomas: Black Women's Health Study. *American Journal of Epidemiology* 2014;179:112-119.
8. Eddi R, Karki A, Shah A, et al. Association of type 2 diabetes and colon adenomas. *J Gastrointest Cancer* 2012;43:87-92.
9. Elwing JE, Gao F, Davidson NO, et al. Type 2 diabetes mellitus: the impact on colorectal adenoma risk in women. *Am J Gastroenterol* 2006;101:1866-71.
10. Vu HT, Ufere N, Yan Y, et al. Diabetes mellitus increases risk for colorectal adenomas in younger patients. *World Journal of Gastroenterology : WJG* 2014;20:6946-6952.
11. Wong P, Weiner MG, Hwang W-T, et al. Insulin Therapy and Colorectal Adenomas in Patients with Diabetes Mellitus. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2012;21:1833-1840.
12. Son P, Lane D, Messina C, et al. Impact of Project SCOPE on Racial/Ethnic Disparities in Screening Colonoscopies. *Journal of Racial and Ethnic Health Disparities* 2014;1:110-119.
13. Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Res Clin Pract* 2012;98:271-84.
14. Cho YH, Ko BM, Kim SH, et al. Does metformin affect the incidence of colonic polyps and adenomas in patients with type 2 diabetes mellitus? *Intest Res* 2014;12:139-45.
15. Katz M, Parrish ME, Li E, et al. The Effect of Race/Ethnicity on the Age of Colon Cancer Diagnosis. *J Health Dispar Res Pract* 2013;6:62-69.
16. Singh S, Singh H, Singh PP, et al. Antidiabetic Medications and the Risk of Colorectal Cancer in Patients with Diabetes Mellitus: A Systematic Review and Meta-analysis. *Cancer Epidemiology Biomarkers & Prevention* 2013;22:2258-2268.
17. Zhang Z-J, Zheng Z-J, Kan H, et al. Reduced Risk of Colorectal Cancer With Metformin Therapy in Patients With Type 2 Diabetes: A meta-analysis. *Diabetes Care* 2011;34:2323-2328.
18. Zhao X, Li Y, Chen M, et al. Effects of different doses of metformin treatment for 6 months on aberrant crypt foci in Chinese patients with impaired glucose tolerance. *Eur J Cancer Prev* 2015;24:27-36.
19. Siddiqui AA, Maddur H, Naik S, et al. The association of elevated HbA1c on the behavior of adenomatous polyps in patients with type-II diabetes mellitus. *Dig Dis Sci* 2008;53:1042-7.
20. Siddiqui AA, Spechler SJ, Huerta S, et al. Elevated HbA1c is an independent predictor of aggressive clinical behavior in patients with colorectal cancer: a case-control study. *Dig Dis Sci* 2008;53:2486-94.
21. American Diabetes Association. Standards of Medical Care in Diabetes - 2015. *Diabetes Care* 2015;38:S1-S93.
22. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc* 2015;81:31-53.

## **Budget**

### *Personnel*

<b>Expense</b>	<b>Cost</b>
Research Analyst – Salary	\$8,144.00
Research Analyst – Fringe Benefits	\$4,364.00
Graduate Student – Salary	\$1,200.00
Graduate Student – Fringe Benefits	\$192.00
<b>Total – Personnel</b>	<b>\$13,900.00</b>

*Budget Table 1* – This table includes expenses related to the annual salaries/benefits of the personnel who will be working on the project.

### *Research Costs*

<b>Expense</b>	<b>Per Unit Cost</b>	<b>Cost for 350 Units</b>
Fasting Plasma Glucose Test	\$5.46	\$1,911.00
Hemoglobin A1c Test	\$17.43	\$6,100.50
Insulin Level Test	\$47.00	\$16,450.00
<i>Cost of Test</i>	<i>(\$10.00)</i>	
<i>Handling</i>	<i>(\$37.00)</i>	
<b>Total – Research Costs</b>		<b>\$24,461.50</b>

*Budget Table 2* – This table includes expenses related to the costs of performing the analyses necessary for this project. We will be performing the tests listed in this table on 350 patients per year to obtain preliminary lab results (see justification). The cost per patient is \$69.89.

### *Total Expenses*

<b>Expense</b>	<b>Year 1 Cost</b>	<b>Year 2 Cost</b>
Total Personnel Expenses	\$13,900.00	\$13,900.00
Total Research Costs	\$24,461.50	\$24,461.50
<b>Total Expenses</b>	<b>\$38,361.50</b>	<b>\$38,361.50</b>

*Budget Table 3* – This table includes the total cost of the executing this project.

## **Budget Justification**

### **A. Key Personnel:**

Joshua Miller, M.D., M.P.H. - PI. No salary or fringes are requested.

### **B. Other Personnel:**

1. Matthew Murray, M.S. Research Analyst. He will devote 34% effort and 34% of his salary and fringes (44%) are requested. He has an M.S. from the Department of Biochemistry and Cell Biology at Stony Brook University. He will assist Dr. Miller with the collection of retrospective and prospective data.
2. Xinyu Tian. Graduate student. She will devote 5% effort and 5% of her salary and benefits (15%) are requested. She is a senior graduate student in the Department of Applied Mathematics and Statistics at Stony Brook University, who has extensive experience in analyzing clinical GI studies related to colonic neoplasia. She is jointly mentored by Dr. Wei Zhu, Deputy Chair of the Department of Applied Mathematics and Statistics and Dr. Ellen Li, Chief of Gastroenterology and Hepatology. She will perform the statistical analysis for this project under the supervision of Drs. Zhu and Li.

### **C. Supplies:** none

### **D. Travel:** none

### **E. Other:** \$24,461.50 is requested to obtain preliminary research lab results on 350 patients with diabetes per year undergoing their initial screening colonoscopy. The cost per patient is \$69.89, and includes the following lab testing: Fasting glucose \$5.46; HgbA1c \$17.43; Insulin level \$10 + \$37 handling fee, equating to a cost of \$69.89 per patient.

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Miller, Joshua David	POSITION TITLE Assistant Professor of Medicine Endocrinology and Metabolism Director of Diabetes Care		
eRA COMMONS USER NAME (credential, e.g., agency login) millerjo			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of Rochester	B.A.	08/02	Biology
University of Rochester	M.P.H.	06/04	Health and Aging, Patient Safety
University of Rochester	M.D.	06/08	Distinction in Community Service
Mount Sinai School of Medicine	Internship	06/09	Internal Medicine
Mount Sinai School of Medicine	Residency	06/11	Internal Medicine
Columbia University/NY Presbyterian Hospital	Fellowship	06/14	Endocrinology

### A. Personal Statement

The goal of the proposed research is to expand our knowledge of the association between glycemic control and development of colon cancer in patients with diabetes. The breadth and depth of my personal and professional experiences make me an ideal candidate to carry out this research. Working under the mentorship of Drs. Li and Buscaglia, this multidisciplinary effort will create a powerful resource for the investigation of diabetes as a risk factor for GI malignancy. As diabetes project lead for Suffolk County-wide Medicaid redesign efforts, I have a keen understanding of the population health effects of uncontrolled diabetes and its complications. This project has the potential to greatly inform clinicians in their ability to counsel patients further on health risks related to their disease. Moreover, this project will forge cross-discipline collaboration to further enhance Stony Brook's mission as a Specialized Program of Research Excellence in Human Cancer.

### B. Positions and Honors

#### Positions and Employment

2015-	Director of Diabetes Care	Stony Brook Medicine, Stony Brook, NY
2013-	Assistant Professor of Medicine	Stony Brook Medicine, Stony Brook, NY
2011-13	Clinical/Research Fellow in Endocrinology	Columbia University Medical Center, New York, NY
2008-2011	Intern/Resident in Internal Medicine	Mount Sinai Medical Center, New York, NY

#### Other Experience and Professional Memberships

2015-	Member, American Diabetes Association
2015-	Reviewer - International Journal of Pediatrics. ISSN: 1687-9856
2014-	Project Lead, Delivery System Reform Incentive Payment/DSRIP Suffolk Care Collaborative
2014-	Chair, Young Physicians Section and Member, Suffolk County Medical Society
2011-	Member, American Association of Clinical Endocrinologists
2008-	Member, The Endocrine Society
2008-	Member, New York Academy of Medicine

2004-	Member, Medical Society of the State of New York
2011-13	Member, Type 1 Diabetes Exchange Transition Working Group
2008-14	Member, New York County Medical Society
2004-08	Member, Rochester Academy of Medicine
2004-08	Member, Monroe County Medical Society

### **Honors**

2011 - Swanson Fellow in Diabetes at Columbia University College of Physicians and Surgeons  
 2008 - The Charles D. Kochakian Award in Endocrinology and Nutrition  
 2008 - The Endocrine Society Medical Student Achievement Award  
 2008 - University of Rochester School of Medicine and Dentistry Class of 1954 Scholarship Recipient

### **C. Selected Peer-reviewed Publications**

1. **Miller J**, Richman D. "Preoperative Management of Diabetes." 2016 *Anesthesiology Clinics* 34:155-169.
2. **Miller J**. "Evaluation and Management of the Newly-diagnosed Patient with Type 2 Diabetes" in Davies T. "A Case-Based Guide to Clinical Endocrinology" (2<sup>nd</sup> Edition). Springer, 2015. ISBN 978-1-4939-2059-4.
3. Ebner S, **Miller J**. "Transition to Insulin in Patients with Type 2 Diabetes" in Davies T. "A Case-Based Guide to Clinical Endocrinology" (2<sup>nd</sup> Edition). Springer, 2015. ISBN 978-1-4939-2059-4.
4. **Miller J**, Freeby M, Golden L, Softness B, McMahon D, Bunzel E, and Goland R. 2012. Barriers to successful transition of care in emerging adults with type 1 diabetes. *Diabetes* 61:A634.
5. Messer C, Boston R, Leroith D, Geer E, **Miller J**, Messer M, Futterweit W. 2012. Pancreatic  $\beta$ -cell dysfunction in polycystic ovary syndrome: the role of metformin. *Endocr Pract* 18(5):685-93. PMID 22548946

### **D. Research Support**

#### **Completed Research Support**

T32 DK007271 - Bilezikian (PI)

7/2008 - 6/2013

Training program in Endocrinology and Metabolism

Role: Trainee

Offices for Medical Education Research Grant, University of Rochester

2005

Behavioral change in patients with diabetes

The goal of this project was to evaluate barriers and facilitators to successful behavior change in patients with diabetes.

Role: PI

Stanley Scholars Research Fellowship, Long Island Jewish Medical Center

Weiner (PI)

2003

Improving clinician communication for advance care planning

The goal of this project was to describe emotional, cognitive and skill barriers to shared decision-making with seriously ill patients and their loved ones.

Role: research assistant

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Ellen Li

eRA COMMONS USER NAME (credential, e.g., agency login): ELLENLI1

POSITION TITLE: Professor of Medicine and Microbiology and Molecular Genetics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Stanford University, Stanford, CA	B.S.	1974	Chemistry
Washington University-St. Louis, St. Louis, MO	M.D.	1980	Medicine
Washington University-St. Louis, St. Louis, MO	Ph.D.	1980	Biochemistry
Massachusetts General Hospital, Boston, MA	Residency	1980-1983	Internal Medicine
Barnes Hospital, St. Louis MO	Fellow	1983-1984	Gastroenterology
Washington University-St. Louis, St. Louis, MO	Post-doc	1984-1986	Molecular Biology

### A. Personal Statement

Over the past 11 years the focus of my research efforts has been to build patient data/tissue repositories that will facilitate clinical translational research in digestive diseases. I was the founding Director of the Washington University Digestive Diseases Research Core Center (2000) and the driving force in building its Center's Biobank. While I still continue to commute regularly to St. Louis where I am principally responsible for updating detailed patient clinical data linked to the samples collected there, I have built a parallel infrastructure for collecting linked blood, tissue, and stool in both adult and pediatric patients with digestive diseases at the Stony Brook Medicine. In addition to accumulating samples I have been building an infrastructure to support the bioinformatics and statistical analysis of the data generated by the GI Biobank. I have a particular interest in mentoring students, trainees, and junior faculty who are interested in pursuing a career in clinical translational research.

### B. Positions and Honors

1973	Phi Beta Kappa, Stanford University
1974-1978	Mr. and Mrs. Spencer T. Olin Fellowship for Women in Science
1980	Alpha Omega Alpha
1980-83	Intern and Resident, Medicine, Massachusetts General Hospital, Boston, MA
1983-1986	Fellow in Medicine (Gastroenterology), Washington University School of Medicine
1985-1991	Lucille P. Markey Scholar, 1985
1986-1992	Assistant Professor of Medicine, Washington University, St. Louis, MO
1987-1992	Assistant Professor of Biochemistry and Molecular Biophysics, Washington University
1992-1995	NIH Research Career Development Award DK02072
1992-1997	Associate Professor of Medicine, Washington University, St. Louis, MO
1992-1993	Associate Professor of Biochemistry and Molecular Biophysics, Washington University
1993	GRG-AGA Young Investigator Award
1995-2000	Burroughs Wellcome Fund Toxicology Scholar Award
1996-1997	Co-director, Division of Gastroenterology, Washington University
1997-	Professor of Medicine, Washington University
2000-2009	Director of the Washington University Digestive Diseases Research Core Center

2009-2012	Professor of Medicine and Molecular Genetics and Microbiology, Stony Brook University Stony Brook University Education Opportunities Program/ Advancement on Individual Merit Distinguished Advocate Award
2012-2013	Interim Chief, Division of Gastroenterology and Hepatology, Stony Brook University
2013-	Chief, Division of Gastroenterology and Hepatology, Stony Brook University
2013-2014	SUNY Presidential Fellow, SUNY Health Network of Excellence

### **Other Experience and Professional Memberships**

Member, American Gastroenterological Association, Research Committee, Nominating Committee  
 Member, American Society for Clinical Investigators  
 Member, Association of American Physicians

### **C. Contributions to Science**

**1. Synthesis and processing of N-glycans in N-glycoproteins.** My graduate thesis work with Dr. Stuart Kornfeld focused on elucidating the synthesis of N-glycans in N-glycoproteins.

- Li E**, Kornfeld S. Structure of the altered oligosaccharide present in glycoproteins from a clone of Chinese hamster ovary cells deficient in N-acetylglucosaminyltransferase activity. *J Biol Chem.* 1978;253:6426-31.
- Li E**, Tabas I, Kornfeld S. The synthesis of complex-type oligosaccharides. I. Structure of the lipid-linked oligosaccharide precursor of the complex-type oligosaccharides of the vesicular stomatitis virus G protein. *J Biol Chem.* 1978;253:7762-70.
- Kornfeld S, **Li E**, Tabas I. The synthesis of complex-type oligosaccharides. II. Characterization of the processing intermediates in the synthesis of the complex oligosaccharide units of the vesicular stomatitis virus G protein. *J Biol Chem.* 1978;253:7771-8.
- Li E**, Kornfeld S. Structural studies of the major high mannose oligosaccharide units from Chinese hamster ovary cell glycoproteins. *J Biol Chem.* 1979;254:1600-5.

**2. Structure and function of cellular and nuclear retinoid binding proteins.** As a postdoctoral fellow in Dr. Jeffrey Gordon's laboratory I cloned an intestinal cellular retinol binding protein 2 (CRBP2). I then went on to examine the structure of cellular retinol binding proteins and nuclear binding proteins such as retinoid-X-receptor using fluorescence and nuclear magnetic resonance. I examined the function of CRBP2 by generating a knockout mouse.

- Lu J, Lin CL, Tang C, Ponder JW, Kao JL, Cistola DP, **Li E**. Binding of retinol induces changes in rat cellular retinol-binding protein II conformation and backbone dynamics. *J Mol Biol.* 2000;300:619-32.
- E X, Zhang L, Lu J, Tso P, Blaner WS, Levin MS, **Li E**. Increased neonatal mortality in mice lacking cellular retinol-binding protein II. *J Biol Chem.* 2002 ;277:36617-23.
- Lu J, Cistola DP, **Li E**. Analysis of ligand binding and protein dynamics of human retinoid X receptor alpha ligand-binding domain by nuclear magnetic resonance. *Biochemistry.* 2006;45:1629-39.
- Lu J, Dawson MI, Hu QY, Xia Z, Dambacher JD, Ye M, Zhang XK, **Li E**. The effect of antagonists on the conformational exchange of the retinoid X receptor alpha ligand-binding domain. *Magn Reson Chem.* 2009;47:1071-80. PMC3436934

**3. Molecular pathogenesis of *Entamoeba histolytica*.** As a junior faculty member, I shared a laboratory with my husband Dr. Samuel L. Stanley and collaborated on studies on the molecular pathogenesis of *Entamoeba histolytica*, an intestinal protozoan parasite.

- Li E**, Becker A, Stanley SL Jr. Use of Chinese hamster ovary cells with altered glycosylation patterns to define the carbohydrate specificity of *Entamoeba histolytica* adhesion. *J Exp Med.* 1988;167:1725-30.
- Stanley SL Jr, Becker A, Kunz-Jenkins C, Foster L, **Li E**. Cloning and expression of a membrane antigen of *Entamoeba histolytica* possessing multiple tandem repeats. *Proc Natl Acad Sci U S A.* 1990;87:4976-80.
- Stanley SL Jr, Tian K, Koester JP, **Li E**. The serine-rich *Entamoeba histolytica* protein is a phosphorylated membrane protein containing O-linked terminal N-acetylglucosamine residues. *J Biol Chem.* 1995;270:4121-6.

**4. Integrative analysis of host genetic environmental and microbial factors in GI disorders.** Over the past 11 years I have been engaged in prospectively biobanking patient tissues, blood and stool to launch collaborative clinical translational studies to examine interactions between host genomic alterations, environmental factors and the microbiome in GI disorders.

- a. Cadwell K, Liu J, Brown SL, Miyoshi H, Loh J, Lennerz J, Kishi C, Carrero JA, Hunt S, Stone C, Brunt EM, Sleckman B, Li E, Mizushima N, Stappenbeck TS, Virgin HW 4th. A key role for autophagy and the autophagy gene Atg16L1 in murine and human intestinal Paneth cells. *Nature*. 2008; 456: 259-63. PMC: 2695978.
- b. Chen H, Lee A, Bowcock A, Zhu W, Li E, Ciorba M, Hunt S. Influence of Crohn's disease risk alleles and smoking on disease location. *Dis Colon Rectum*. 2011;54:1020-5. PMC3403696
- c. Li E, Hamm CM, Gulati AS, Sartor RB, Chen H, Wu X, Zhang T, Rohlf FJ, Zhu W, Gu C, Robertson CE, Pace NR, Boedeker EC, Harpaz N, Yuan J, Weinstock GM, Sodergren E, Frank DN. Inflammatory bowel diseases phenotype, *C. difficile* and NOD2 genotype are associated with shifts in human ileum associated microbial composition. *PLoS ONE*, 2012; 7:e26284 PMC3374607
- d. Zhang T, DeSimone RA, Jiao X, Rohlf FJ, Zhu W, Gong Q, Hunt SR, Dassopoulos T, Newberry RD, Sodergren E, Weinstock G, Robertson CE, Frank DN, Li E. Host genes related to Paneth cells and xenobiotic metabolism are associated with shifts in human ileum-associated microbial composition. *PLoS ONE*, 2012; 7:e30044 PMC3374611
- e. Li E, Ji P, Ouyang N, Zhang Y, Wang XY, Rubin DC, Davidson NO, Bergamaschi R, Shroyer KR, Burke S, Zhu W, Williams JL. Differential expression of miRNAs in colon cancer between African and Caucasian Americans: implications for cancer racial health disparities. *Int J Oncol*. 2014;45:587-94. PMC4091964
- f. Son P, Lane DS, Messina CR, Yang J, Zhu J, Li E, Nagula S, Lascarides CE, Bucobo JC. Impact of Project SCOPE on racial/ethnic disparities in screening colonoscopies. *J Racial Ethnic Health Disparities*. 2014; 1:110–119
- g. Son JS, Khair S, Pettet DW 3rd, Ouyang N, Tian X, Zhang Y, Zhu W, Mackenzie GG, Robertson CE, Ir D, Frank DN, Rigas B, Li E. Altered Interactions between the Gut Microbiome and Colonic Mucosa Precede Polyposis in APCMin/+ Mice. *PLoS ONE*. 2015;10:e0127985. PMC4485894
- h. Son JS, Zheng LJ, Rowehl LM, Tian X, Zhang Y, Zhu W, Litcher-Kelly L, Gadow KD, Gathungu G, Robertson CE, Ir D, Frank DN, Li E. Comparison of Fecal Microbiota in Children with Autism Spectrum Disorders and Neurotypical Siblings in the Simons Simplex Collection. *PLoS ONE*. 2015;10:e0137725. PMC3252763
- i. Zhang Y, Rowehl L, Krumsiek JM, Orner EP, Shaikh N, Tarr PI, Sodergren E, Weinstock GM, Boedeker EC, Xiong X, Parkinson J, Frank DN, Li E. Identification of Candidate Adherent-Invasive *E. coli* Signature Transcripts by Genomic/Transcriptomic Analysis. *PLoS ONE* 2015;10: e0134759. PMC4509574
- j. Wang X, Yu X, Zhu W, McCombie WR, Antoniou E, Powers RS, Davidson NO, Li E, Williams J. A trimming-and-retrieving alignment scheme for reduced representation bisulfite sequencing. *Bioinformatics*. 2015;31:2040-2. PMC Journal – In Process.



May 5, 2016

Linda M. Obeid, M.D.  
Dean of Research  
Stony Brook University School of Medicine  
Stony Brook, NY 11794

Re: FUSION Seed-Grant Award

Dear Committee Members,

I am pleased to offer my support for Dr. Joshua Miller's FUSION Seed-Grant application entitled "Diabetes, glycemic control & progression to colon cancer." Dr. Miller is Assistant Professor of Medicine in the Division of Endocrinology, Director of Diabetes Care for Stony Brook Medicine and is currently leading the Diabetes project in DSRIP. Diabetes is a major risk factor for colon cancer and I believe that using colonoscopy as a point of entry will help reduce diabetes complications and help us to better risk stratify patients with respect to different colon cancer modalities.

Dr. Buscaglia, Dr. Miller's faculty mentor, encouraged Dr. Miller to develop a clinical translational project related to colon cancer screening. Drs. Miller and Buscaglia have assembled a team including Stony Brook Medicine faculty from multiple divisions, medical students, internal medicine residents and GIfellows. This seed award was developed in the course of several GI research meetings and builds upon the results of previous Department of Medicine Seed Awards (Bucobo, Kravets). Please note that these previous seed awards contributed to our ability to successfully compete for an NCI P20 award.

As the Director of the GI Biobank, I will support Dr. Miller's collection of retrospective and prospective data on patients undergoing initial colonoscopy. I believe this data will help Dr. Miller develop a project competitive for extramural funding. We have been rapidly expanding our screening colonoscopy volume (one of the fastest growing sections of SBUH this past year) and it is important that we capture the data to demonstrate our ability to deliver quality care.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Ellen Li".

Ellen Li, M.D., Ph.D.

Director, Digestive Diseases Research Tissue Procurement Facility  
Chief, Division of Gastroenterology and Hepatology

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Jonathan M. Buscaglia, MD, FASGE	POSITION TITLE Associate Professor of Medicine		
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Union College, Schenectady, New York	B.S.	06/1997	Biology and Psychology
State University of New York at Buffalo	M.D.	05/2001	Medicine
Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY		06/2004	Internal Medicine
Johns Hopkins University School of Medicine, Johns Hopkins Hospital, Baltimore, MD		06/2008	Gastroenterology and Therapeutic Endoscopy

### A. Personal Statement

For the extent of my career in gastroenterology, both my clinical and my research focus have centered upon advanced endoscopic techniques, as well as the detection of GI malignancies. As a result, I was extremely enthusiastic when Dr. Joshua Miller approached me with his desire to utilize colon cancer screening and colonoscopy as a gateway for examining the risk of pre-cancerous and cancerous neoplasia in diabetic patients. I have worked with Josh over the past several months in crystalizing his research ideas that link diabetes and colorectal cancer; and therefore I am extremely excited to continue to work alongside him as he initiates all the stages of this very important research study.

### B. Positions and Honors

2007-2008	Instructor of Medicine, Therapeutic Endoscopy Fellow; Johns Hopkins University School of Medicine, Johns Hopkins Hospital, Baltimore, Maryland
2008-2013	Assistant Professor of Medicine; State University of New York, Stony Brook University Medical Center, Stony Brook, New York
2008-2011	Visiting Johns Hopkins
2013-Pres	Associate Professor of Medicine; State University of New York, Stony Brook University Medical Center, Stony Brook, New York

### Academic Appointments of Distinction:

2014-2017	Editorial Board (Associate Editor), <i>Clinical Gastroenterology and Hepatology (CGH)</i>
2015-2016	Vice President, New York Society for Gastrointestinal Endoscopy (NYSGE)
2014-2017	Member, ASGE Quality in Endoscopy Committee
2014-2016	Member, AGA Grant Review Committee
2011-2014	Member, ASGE Research Committee
2014-Pres	ASGE Taskforce on Endoscope Reprocessing and Infection Transmission
2012-2014	VideoGIE Editorial Board, <i>Gastrointestinal Endoscopy</i>

### C. Contributions to Science

(10 most relevant peer-review research publications in chronological order, from 71 total)

1. Giday SA, Magno P, Gabrielson KL, **Buscaglia JM**, Canto MI, Ko CW, Clarke JO, Kalloo AN, Jagannath SB, Shin EJ, Kantsevov SV. The utility of contrast-enhanced endoscopic ultrasound in monitoring ethanol-induced pancreatic tissue ablation: a pilot study in a porcine model. *Endoscopy* 2007; 39:525-9.
2. Magno P, Giday SA, Gabrielson KL, Shin EJ, **Buscaglia JM**, Clarke JO, Ko CW, Jagannath SB, Canto MI, Sedrakyan G, Kantsevov SV. Endoscopic ultrasound (EUS)-guided implantation of radio-opaque marker into mediastinal and celiac lymph nodes is safe and effective. *Gastrointestinal Endosc* 2007; 66(2):387-92.
3. Magno P, Ko CW, **Buscaglia JM**, Giday SA, Jagannath SB, Clarke JO, Shin EJ, Kantsevov SV. Endoscopic ultrasound (EUS)-guided angiography: a novel approach to diagnostic and therapeutic interventions in the vascular system. *Gastrointestinal Endosc* 2007; 66:587-91.
4. Giday SA, Ko CW, Clarke JO, Shin EJ, Magno P, Jagannath SB, **Buscaglia JM**, Kantsevov SV. Endoscopic ultrasound (EUS)-guided portal vein CO2 angiography: a pilot study in a porcine model. *Gastrointest Endosc* 2007; 66(4):814-819.
5. Giday SA, Clarke JO, **Buscaglia JM**, Shin EJ, Jagannath SB, Canto MI, Ko CW, Magno P, Kantsevov SV. Endoscopic ultrasound (EUS)-guided portal vein catheterization: a novel promising approach for portal angiography and portal vein pressure measurements. *Gastrointestinal Endosc* 2008; 67:338-342.
6. Magno P, Giday SA, Gabrielson KA, Shin EJ, Clarke JO, Ko CW, **Buscaglia JM**, Jagannath SB, Canto MI, Kantsevov SV. EUS-guided submucosal implantation of a radiopaque marker: a simple and effective procedure to facilitate subsequent surgical and radiation therapy. *Gastrointest Endosc* 2008; 67(7):1147-1152.
7. **Buscaglia JM**, Giday SA, Kantsevov SV, Jagannath SB, Magno P, Wolfgang CL, Daniels JA, Canto MI, Okolo PI. Patient-related and cyst-related factors for improved prediction of malignancy within cystic lesions of the pancreas. *Pancreatology* 2009; 9(5):631-638.
8. **Buscaglia JM**, Dray X, Shin, EJ, Magno P, Chmura KM, Surti VC, Dillon TE, Ducharme MS, Donatelli G, Thuluvath PJ, Giday SA, Kantsevov SV. A New Alternative for TIPSS: EUS-Guided Creation of Intrahepatic Porto-Systemic Shunt (With Videos). *Gastrointest Endosc* 2009; 69(4):941-7.
9. **Buscaglia JM**, Shin EJ, Giday SA, Kapoor S, Dunbar KB, Eloubeidi MA, Canto MI, Jagannath SB. Awareness of guidelines and trends in management of suspected pancreatic cystic neoplasms: survey results among general gastroenterologists and EUS specialists. *Gastrointest Endosc* 2009; 69(4):813-20.
10. DiMaio CJ, **Buscaglia JM**, Gross SA, Aslanian HR, Goodman AJ, Ho S, Kim MK, Pais S, Schnoll-Sussman F, Sethi A, Siddiqui UD, Robbins DH, Adler DG, Nagula S. Practice patterns in FNA technique: A survey analysis. *World J Gastrointest Endosc* 2014; 6(10):499-505.

#### **D. Research Support**

Completed Research Support:

State University of New York, Targeted Research Opportunities (TRO) Program	2009-2011
FUSION Seed Grant Award, \$80,000	
Development of novel nano-sensors for cancer biomarkers within pancreatic cystic lesions	
Role: PI	

American Society for Gastrointestinal Endoscopy (ASGE), Endoscopic Research Award	2015-2016
Award, \$75,000	
Pancreatic organoids from EUS-guided core biopsy: assembling a living biobank of resectable and non-resectable pancreatic cancers.	
Role: PI	



May 05, 2016

Dear Committee Members,

I am honored to write this letter in support of Dr. Joshua Miller's application for a Department of Medicine Fusion Seed Grant. I have served as Dr. Miller's faculty mentor since shortly after his arrival to Stony Brook two years ago. In that time, I have seen Dr. Miller's academic career grow and thrive. His academic interests in diabetes care and population health have flourished here at Stony Brook, as Dr. Miller has successfully lead our institution's efforts towards improving care for countless people with diabetes.

Through Dr. Miller's leadership in our DSRIP Diabetes Project, he has developed novel approaches to improving care for people with diabetes throughout Suffolk County. One of the missions of the DSRIP program is to enhance primary and secondary preventive care for patients with chronic disease. The project proposed by Dr. Miller and our team addresses these goals by directly expanding on our knowledge of the effects of glycemic control on risk of colon cancer. Given the existing data in this area, I am confident that our work will further establish a connection between diabetes and GI malignancy. This will help to inform countless clinicians as they counsel their patients with diabetes on the importance of better glucose control. Furthermore, this work may substantially impact current colon cancer screening guidelines for patients with diabetes.

One of the goals of our division's research has been to foster an environment of multidisciplinary collaboration. As a member of the Endocrine Division, Dr. Miller brings to our team a unique skillset related to diabetes care in addition to his public health and research expertise. Seed funding from the Department of Medicine will prove tremendously valuable in advancing Dr. Miller's career goals as an academic physician, as well as providing support for an area of research potentially impacting millions of people with diabetes. I am very excited and looking forward to collaborating with him on this project.

Sincerely,

A large, stylized handwritten signature in black ink, likely belonging to Jonathan M. Buscaglia.

A small, handwritten set of initials "MD" in black ink, likely representing a medical professional.

**Jonathan M. Buscaglia, MD, FASGE**

Associate Professor of Clinical Medicine

Division of Gastroenterology and Hepatology

Stony Brook University School of Medicine

*School of Medicine*

*Professor of Medicine and Dean  
of Research*  
**Lina M. Obeid, M.D.**

July 5, 2016

Joshua D. Miller, MD, MPH  
Assistant Professor, Department of Medicine  
Stony Brook Medicine  
26 Research Way  
Stony Brook, NY 11794-8154

Re: 2016/2017 Targeted Research Opportunity Program – Clinical Research Awards

Dear Dr. Miller:

Thank you for your application entitled, “Diabetes, glycemic control & progression to colon cancer”. We received many outstanding applications. The applications have been reviewed and I am pleased to inform you that your application has been selected for a TRO 2016/2017 award with matching support as outlined below. These funds are made available to you through the Targeted Research Opportunities Program to support the activities as outlined in your proposal. This commitment is contingent upon full realization of all other pledges indicated below.

\$ 30,000 - School of Medicine, Office of Scientific Affairs

\$ 10,000 - Department of Medicine

On behalf of the University, I wish to congratulate you on receiving this award. In order to process the award you must establish a TRO Central User ID and PIN number prior to the award activation. Please contact David Cyrille at 631-444-7399 or e-mail: [David.Cyrille@Stonybrook.edu](mailto:David.Cyrille@Stonybrook.edu) to create these login credentials. Before these funds can be made available to you, please complete the attached TRO compliance form and mail it back to [Stacey.Hondropulos@stonybrookmedicine.edu](mailto:Stacey.Hondropulos@stonybrookmedicine.edu) by July 15, 2016. A progress report on the research supported by this award will be required 12 months from the date of the award activation. Finally, please note that any unobligated funds remaining in this account three months after the award completion date will be returned to the School of Medicine. Publications resulting from this award should acknowledge the Stony Brook School of Medicine.

Sincerely,



Lina M. Obeid, M.D.  
Professor of Medicine  
Dean of Research, School of Medicine

## **Title: Stony Brook GI Biobank**

### **Abstract**

The Stony Brook GI Biobank is a continuation of the Stony Brook Digestive Diseases Research Tissue Procurement Facility, which has been supported by the Simons Foundation since 2010. The GI Biobank operates as an organ specific module under the umbrella of the Stony Brook Medicine Biobank, directed by Dr. Ken Shroyer, Chair of Pathology and operates under the institutional New York State Biobank License issued for Stony Brook University. The collection of biospecimens (tissue, blood, stool) has been organized along the clinical service line devoted towards treating patients with GI disorders. Thus the collection effort represents an interdepartmental effort between adult and pediatric gastroenterologists and GI surgeons. Specimens are stripped of identifying information and linked by a sample and patient code to rigorously defined clinical endpoints. The GI Biobank serves as the linchpin for launching clinical translational pilot projects. In addition, the GI Biobank provides faculty users with bioinformatics and statistical support. The GI Biobank is in the process of building an integrative bioinformatic platform that links data (primarily sequencing and microarray data) generated from GI biobank specimens to longitudinal clinical data. The pilot data and publications generated by the GI Biobank was key to our ability to secure NCI funding for a collaborative P20 planning grant entitled "Partnership to study racial/ethnic differences in GI cancer biology". The funding we are requesting over the next three years is to support the GI Biobank staff required to sustain the collection, bioinformatics and statistical services we provide to Stony Brook investigators and their collaborators to carry out pilot clinical translational research in GI disorders.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Ellen Li

eRA COMMONS USER NAME (credential, e.g., agency login): ELLENLI1

POSITION TITLE: Professor of Medicine and Microbiology and Molecular Genetics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Stanford University, Stanford, CA	B.S.	1974	Chemistry
Washington University-St. Louis, St. Louis, MO	M.D.	1980	Medicine
Washington University-St. Louis, St. Louis, MO	Ph.D.	1980	Biochemistry
Massachusetts General Hospital, Boston, MA	Residency	1980-1983	Internal Medicine
Barnes Hospital, St. Louis MO	Fellow	1983-1984	Gastroenterology
Washington University-St. Louis, St. Louis, MO	Post-doc	1984-1986	Molecular Biology

**A. Personal Statement**

Over the past nine years the focus of my research efforts has been to build patient data/tissue repositories that will facilitate clinical translational research in digestive diseases. I was the founding Director of the Washington University Digestive Diseases Research Core Center (2000) and the driving force in building its Center's Biobank. While I still continue to commute regularly to St. Louis where I am principally responsible for updating detailed patient clinical data linked to the samples collected there, I have built a parallel infrastructure for collecting linked blood, tissue, and stool in both adult and pediatric patients with digestive diseases at the Stony Brook Medicine. The GI biobanking effort at Stony Brook Medicine has been largely supported by the Simons Foundation over the past 5 years. This effort has launched a number of collaborative clinical translational projects that link genomic data to detailed clinical phenotyping information, and led to us successfully competing for a NCI funded planning grant to build a collaborative partnership between Stony Brook University, SUNY Downstate Medical Center with the NCI-funded Cancer Center at Cold Spring Harbor Laboratories to study racial/ethnic differences in GI cancer biology.

**B. Positions and Honors**

1973	Phi Beta Kappa, Stanford University
1974-1978	Mr. and Mrs. Spencer T. Olin Fellowship for Women in Science
1980	Alpha Omega Alpha
1980-83	Intern and Resident, Medicine, Massachusetts General Hospital, Boston, MA
1983-1986	Fellow in Medicine (Gastroenterology), Washington University School of Medicine
1985-1991	Lucille P. Markey Scholar, 1985
1986-1992	Assistant Professor of Medicine, Washington University, St. Louis, MO
1987-1992	Assistant Professor of Biochemistry and Molecular Biophysics, Washington University
1992-1995	NIH Research Career Development Award DK02072
1992-1997	Associate Professor of Medicine, Washington University, St. Louis, MO
1992-present	Associate Professor of Biochemistry and Molecular Biophysics, Washington University
1993	GRG-AGA Young Investigator Award
1995-2000	Burroughs Wellcome Fund Toxicology Scholar Award
1996-1997	Co-director, Division of Gastroenterology, Washington University
1997-present	Professor of Medicine, Washington University
2000-2009	Director of the Washington University Digestive Diseases Research Core Center
2009-present	Professor of Medicine and Molecular Genetics and Microbiology, Stony Brook University
2012	Stony Brook University Education Opportunities Program/ Advancement on Individual Merit

Distinguished Advocate Award  
 2012-2013 Interim Chief, Division of Gastroenterology and Hepatology, Stony Brook University  
 2013-present Chief, Division of Gastroenterology and Hepatology, Stony Brook University  
 2013-2014 SUNY Presidential Fellow, SUNY Health Network of Excellence

### **Other Experience and Professional Memberships**

Member, American Gastroenterological Association, Research Committee  
 Member, American Society for Clinical Investigators  
 Member, Association of American Physicians

### **C. Contributions to Science**

**1. Synthesis and processing of N-glycans in N-glycoproteins.** My graduate thesis work with Dr. Stuart Kornfeld focused on elucidating the synthesis of N-glycans in N-glycoproteins.

- a. **Li E**, Kornfeld S. Structure of the altered oligosaccharide present in glycoproteins from a clone of Chinese hamster ovary cells deficient in N-acetylglucosaminyltransferase activity. *J Biol Chem.* 1978;253:6426-31.
- b. **Li E**, Tabas I, Kornfeld S. The synthesis of complex-type oligosaccharides. I. Structure of the lipid-linked oligosaccharide precursor of the complex-type oligosaccharides of the vesicular stomatitis virus G protein. *J Biol Chem.* 1978;253:7762-70.
- c. Kornfeld S, **Li E**, Tabas I. The synthesis of complex-type oligosaccharides. II. Characterization of the processing intermediates in the synthesis of the complex oligosaccharide units of the vesicular stomatitis virus G protein. *J Biol Chem.* 1978;253:7771-8.
- d. **Li E**, Kornfeld S. Structural studies of the major high mannose oligosaccharide units from Chinese hamster ovary cell glycoproteins. *J Biol Chem.* 1979;254:1600-5.

**2. Structure and function of cellular and nuclear retinoid binding proteins.** As a postdoctoral fellow in Dr. Jeffrey Gordon's laboratory I cloned an intestinal cellular retinol binding protein 2 (CRBP2). I then went on to examine the structure of cellular retinol binding proteins and nuclear binding proteins such as retinoid-X-receptor using fluorescence and nuclear magnetic resonance. I examined the function of CRBP2 by generating a knockout mouse.

- a. Lu J, Lin CL, Tang C, Ponder JW, Kao JL, Cistola DP, **Li E**. Binding of retinol induces changes in rat cellular retinol-binding protein II conformation and backbone dynamics. *J Mol Biol.* 2000;300:619-32.
- b. E X, Zhang L, Lu J, Tso P, Blaner WS, Levin MS, **Li E**. Increased neonatal mortality in mice lacking cellular retinol-binding protein II. *J Biol Chem.* 2002 ;277:36617-23.
- c. Lu J, Cistola DP, **Li E**. Analysis of ligand binding and protein dynamics of human retinoid X receptor alpha ligand-binding domain by nuclear magnetic resonance. *Biochemistry.* 2006;45:1629-39.
- d. Lu J, Dawson MI, Hu QY, Xia Z, Dambacher JD, Ye M, Zhang XK, **Li E**. The effect of antagonists on the conformational exchange of the retinoid X receptor alpha ligand-binding domain. *Magn Reson Chem.* 2009;47:1071-80. PMC3436934

**3. Molecular pathogenesis of *Entamoeba histolytica*.** As a junior faculty member, I shared a laboratory with my husband Dr. Samuel L. Stanley and collaborated on studies on the molecular pathogenesis of *Entamoeba histolytica*, an intestinal protozoan parasite.

- a. **Li E**, Becker A, Stanley SL Jr. Use of Chinese hamster ovary cells with altered glycosylation patterns to define the carbohydrate specificity of *Entamoeba histolytica* adhesion. *J Exp Med.* 1988;167:1725-30.
- b. Stanley SL Jr, Becker A, Kunz-Jenkins C, Foster L, **Li E**. Cloning and expression of a membrane antigen of *Entamoeba histolytica* possessing multiple tandem repeats. *Proc Natl Acad Sci U S A.* 1990;87:4976-80.
- c. Stanley SL Jr, Tian K, Koester JP, **Li E**. The serine-rich *Entamoeba histolytica* protein is a phosphorylated membrane protein containing O-linked terminal N-acetylglucosamine residues. *J Biol Chem.* 1995;270:4121-6.

**4. The effect of genetic factors on host-microbial interactions in GI disorders.** Over the past 10 years I have been engaged in prospectively biobanking patient tissues, blood and stool to launch collaborative clinical translational studies to investigate the role of genetic factors on host-microbial interactions in GI disorders.

- a. Cadwell K, Liu J, Brown SL, Miyoshi H, Loh J, Lennerz J, Kishi C, Carrero JA, Hunt S, Stone C, Brunt EM, Sleckman B, **Li E**, Mizushima N, Stappenbeck TS, Virgin HW 4th. A key role for autophagy and the autophagy gene Atg16L1 in murine and human intestinal Paneth cells. *Nature*. 2008; 456: 259-63. PMC: 2695978.
- b. **Li E**, Hamm CM, Gulati AS, Sartor RB, Chen H, Wu X, Zhang T, Rohlf FJ, Zhu W, Gu C, Robertson CE, Pace NR, Boedeker EC, Harpaz N, Yuan J, Weinstock GM, Sodergren E, Frank DN. Inflammatory bowel diseases phenotype, *C. difficile* and NOD2 genotype are associated with shifts in human ileum associated microbial composition. *PLoS One*, 2012; 7:e26284 PMC3374607
- c. Zhang T, DeSimone RA, Jiao X, Rohlf FJ, Zhu W, Gong Q, Hunt SR, Dassopoulos T, Newberry RD, Sodergren E, Weinstock G, Robertson CE, Frank DN, **Li E**. Host genes related to Paneth cells and xenobiotic metabolism are associated with shifts in human ileum-associated microbial composition. *PLoS One*, 2012; 7:e30044 PMC3374611
- d. Son JS, Khair S, Pettet DW 3rd, Ouyang N, Tian X, Zhang Y, Zhu W, Mackenzie GG, Robertson CE, Ir D, Frank DN, Rigas B, **Li E**. Altered Interactions between the Gut Microbiome and Colonic Mucosa Precede Polyposis in APCMin/+ Mice. *PLoS One*. 2015;10:e0127985. PMC4485894
- e. Son JS, Zheng LJ, Rowehl LM, Tian X, Zhang Y, Zhu W, Litcher-Kelly L, Gadow KD, Gathungu G, Robertson CE, Ir D, Frank DN, **Li E**. Comparison of Fecal Microbiota in Children with Autism Spectrum Disorders and Neurotypical Siblings in the Simons Simplex Collection. *PLoS One*. 2015;10:e0137725.

## **D. Research Support**

### **Ongoing Research Support**

NIH P20 CA192994 Li (PI)

09/23/15-08/31/19

1/2: Partnership to study racial/ethnic differences in GI cancer biology

The goals of this award are to build a collaborative partnership between two SUNY medical campuses, Stony Brook Medicine and SUNY Downstate, with the NCI designated Cancer Center at Cold Spring Harbor Laboratories (CSHL), to evaluate biological and genetic differences in GI cancers (colorectal and pancreatic) that may link to differences in cancer incidence and outcome observed in racial and ethnic minorities. The goal is to augment the representation of underrepresented minorities in the collection of biospecimens and linked high dimensional 'omic datasets generated from these biospecimens. We are committed to improving the participation of underrepresented minorities in biomedical research and in increasing awareness of health disparities among established cancer researchers. The two SUNY medical campuses, will partner with CSHL to create an integrated doctoral certificate program, scholars in BioMedical science in Cancer Health Disparities. This program is designed to engage doctoral students in translational medicine, particularly in cancer health disparities, by promoting understanding of the presentation, progression and treatment of diseases related to the area of their thesis research. The program requires the addition of a clinical co-mentor to the usual student-basic science advisor team who will help guide the student's biomedical/clinical research and immerse the student in clinical experiences, vocabulary and the overall culture of clinical research.

Role: PI

### **Completed Research Support**

SFARI Grant Number: 239729 (Li)

10/1/2012-09/30/2014

Autism, GI symptoms and the enteric microbiota

This study aims to characterize the fecal microbiota and functional GI symptoms in the autism proband and the unaffected sibling of ~300 families registered within the Simons Simplex Collection (SSC) that have consented for recontact.

Role: PI

Crohn's Colitis Foundation of America (Sartor)

1/01/11-12/31/13

Influence of Crohn's- related genetic defects in innate immune function on intestinal microbial composition and function.

Focused on correlating results of genetic animal studies and pediatric patient based samples, on the effect of

Crohn's related genetic defects in innate immune function.

Role: Co-PI

Sinai-Helmsley Alliance for Research Excellence (Sartor)

2012-12/31/13

Postoperative recurrence of Crohn's disease

To analyze ileal microbiota from ileal CD patients undergoing ileo-colic resection recruited through SHARE participants to test the hypothesis that decreased Faecalibacterium spp are associated with an increased risk of endoscopic recurrence.

Role: co-investigator

Simons Foundation (Li)

9/2009-8/2012

Establishing a Digestive Diseases Research Tissue Procurement Facility

Building an infrastructure for prospective collection of clinical data linked to blood and tissue samples in patients with digestive diseases.

Role: PI

1UH2DK083994-01 (Li)

06/01/09-05/31/12

Effect of Crohn's Disease Risk Alleles on Enteric Microbiota

Determine the effect of Crohn's disease risk alleles on ileal mucosal associated bacteria in patients with ileal Crohn's disease, patients with inflammatory bowel diseases not affecting the ileum and patients without inflammatory bowel diseases.

Role: PI

**DETAILED BUDGET FOR INITIAL BUDGET PERIOD  
DIRECT COSTS ONLY**FROM  
11/01/15THROUGH  
10/31/16List PERSONNEL (*Applicant organization only*)

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested (*omit cents*) for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnth	Acad. Mnth	Summer Mnth	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Ellen Li, M.D.-Ph.D.	PD/PI	0.12				0	0	0
Yuanhao Zhang, Ph.D.	Post-doctoral fellow	9			60,000	45,000	20,250	65,250
Suman Grewal, Ph.D.	Study coordinator	7.56			68,000	42,840	19,278	62,118
Leahana Rowehl, M.S.	Technician	9				31,350	14,108	45,458
<b>SUBTOTALS</b>						119,190	53,636	172,826

CONSULTANT COSTS

EQUIPMENT (*Itemize*)SUPPLIES (*Itemize by category*)

15,000

TRAVEL

INPATIENT CARE COSTS

OUTPATIENT CARE COSTS

ALTERATIONS AND RENOVATIONS (*Itemize by category*)OTHER EXPENSES (*Itemize by category*)

Publication 1000

New York Genome Sequencing Center and other expenses 8,901

98,901

CONSORTIUM/CONTRACTUAL COSTS

DIRECT COSTS

30,000

**SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD** (*Item 7a, Face Page*)**\$ 227,727**

CONSORTIUM/CONTRACTUAL COSTS

FACILITIES AND ADMINISTRATIVE COSTS

**TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD****\$ 227,727**

**BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD  
DIRECT COSTS ONLY**

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD (from Form Page 4)	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: <i>Salary and fringe benefits. Applicant organization only.</i>	172,826	172,826	172,826		
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES	15,000	15,000	15,000		
TRAVEL					
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES	9,901	11,174	11,174		
DIRECT CONSORTIUM/ CONTRACTUAL COSTS	30,000	30,000	30,000		
<b>SUBTOTAL DIRECT COSTS</b> (Sum = Item 8a, Face Page)	227,727	230,000	230,000		
F&A CONSORTIUM/ CONTRACTUAL COSTS					
<b>TOTAL DIRECT COSTS</b>	227,727	230,000	230,000		
<b>TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD</b>					<b>\$ 697,727</b>

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

See next page.

**Key Personnel:**

1. Ellen Li, M.D.-Ph.D., PI. She will devote .12 calendar months effort and no salary or fringes is requested. She is responsible for overall operation of the GI Biobank. She meets with individual investigators to discuss collaborative pilot clinical translational projects.

**Other Personnel:**

1. Suman Grewal, Ph.D. Study Coordinator. She will devote 7.56 calendar months effort and 7.56 calendar months of her salary and fringes are requested for three years. She is responsible for consenting and tracking the patients recruited for the GI Biobank.
2. Yuanhao Zhang, Ph.D. Post-Doctoral Fellow. He will devote 9 calendar months effort and 9 calendar months of his salary and fringes are requested over three years. His Ph.D. thesis has focused on integrating of sequencing data generated from multiple platforms. He is responsible for assisting GI Biobank users with bioinformatics and statistical analysis of the data generated from samples collected by the GI Biobank.
3. Leahana Rowehl, M.S. Technician. Ms. Rowehl will devote 9 calendar months and the corresponding months of her salary and fringes are requested for each year. Ms. Rowehl is responsible for processing the clinical samples collected through the GI Biobank for extraction of DNA RNA, generating cDNA conducting PCR analysis.

**Supplies:**

\$15,000 is requested for stool collection kits, blood tubes, RNA stabilization solution, fecal nucleic acid extraction kits, molecular biology reagents, plastic ware.

**Other Expenses:**

1. Publications \$1,000 is requested for publications of preliminary studies generated by the GI Biobank.
2. Sequencing \$8,901 is requested in the initial year for generating preliminary sequencing (metagenomics and metatranscriptomic) data at Cold Spring Harbor Laboratories or New York Genome Center, genotyping data. \$11,174 is requested in years two and three.
3. Subcontract to U. of Colorado. \$30,000 is requested in direct funds to Dr. Daniel Frank's laboratory, who is a long standing collaborator with Dr. Li on the microbiome studies for carrying out 16S rRNA sequencing studies and interpretation of metagenomics and metatranscriptomic studies.

## Specific Aims

The Stony Brook GI Biobank (formerly the Stony Brook Digestive Diseases Research Tissue Procurement Facility) operates as an organ specific module under the umbrella of the Stony Brook Medicine Biobank, directed by Dr. Kenneth Shroyer, Chair of Pathology and thus operates under the institutional New York State Biobank License issued for Stony Brook University. The collection of biospecimens (tissue, blood, stool) has been organized along interdepartmental clinical service lines devoted towards treating patients with GI disorders, particularly GI cancers and inflammatory bowel diseases. The GI Biobank serves as the linchpin for launching collaborative clinical translational pilot projects between clinical and basic investigators that will become competitive for extramural funding. The pilot genomic data and publications generated by the GI Biobank over the previous funding period, contributed to our ability to successfully compete for a collaborative NCI P20 planning grant award entitled “Partnership to study racial/ethnic differences in GI cancer biology”. Over the next funding period, we propose to align the thematic development of collaborative clinical translational projects along the following two **Aims**:

**Aim 1. The effect of diabetes mellitus on colonic neoplasia.** Diabetes mellitus is a risk factor for colon cancer and pancreatic cancer [1-4], and diabetes mellitus is more prevalent in African Americans than Caucasians [5]. Furthermore, the overall prevalence of diabetes is increasing in this country [5]. We speculate that the increased prevalence of diabetes mellitus in African Americans may contribute to the increased incidence and mortality of colon and pancreatic cancer in African Americans [6]. We would like to examine further whether diabetes control and/or diabetes medications to control hyperglycemia influence the risk of developing adenomas, advanced adenomas and colon cancers. The GI Biobank proposes to support collaborative interactions between endocrinologists and gastroenterologists at Stony Brook Medicine to test this hypothesis in both retrospective and prospective analyses of all subjects undergoing screening and surveillance colonoscopy. The preliminary data and publications will be used to develop additional clinical translational projects (minimum of 4), which are required for submission of a collaborative P50 Specialized Programs of Research Excellence (SPORE) in Human Cancer focusing on GI cancers in the next three years.

**Aim 2. Characterizing the effect of fecal microbial transplant on microbial composition and function in patients with recurrent *Clostridium difficile* infection and/or inflammatory bowel diseases.** Alterations in the resident microbial composition of the gastrointestinal tract have been associated with an increasing number of human diseases. In some disorders, such as obesity, reported differences have been poorly reproducible between studies [7]. In contrast, microbiome studies on inflammatory bowel diseases, particularly in Crohn’s disease affecting the ileum have yielded consistent differences [7-15], such as depletion of an anti-inflammatory bacteria, *Faecalibacterium prausnitzii*. What is less clear, is whether these alterations are a result of intestinal inflammation or whether these alterations contribute to perpetuating intestinal inflammation. Other important questions are 1.) whether any intervention can reverse these alterations in the microbiome, and 2.) whether reversing these alterations have any impact on clinical outcome. Fecal microbial transplant from health donors, has emerged as an effective (~90%) intervention for preventing further recurrence of *Clostridia difficile* infections [18]. In our preliminary studies we have noted depletion of *F. prausnitzii* in patients with recurrent *C. difficile* colitis compared to healthy donors. To test the hypothesis that fecal microbial transplant will restore *F. prausnitzii* levels in recurrent *C. difficile* infections and/or inflammatory bowel diseases, and to identify other alterations in microbial composition/function, we plan to characterize the effect of fecal microbial transplant in 90 patients with recurrent *C. difficile* infection and/or inflammatory diseases and their healthy donors, using state of the art 16S rRNA, metagenomics and metatranscriptomic sequencing. This data will be used for submission of grant applications for extramural funding in the next one to two years.

## RESEARCH STRATEGY

### Significance

The Stony Brook GI Biobank serves as the linchpin for launching collaborative clinical translational pilot projects between clinical and basic investigators on GI disorders, particularly GI cancers and inflammatory bowel diseases. Since its inception 5 years ago, linked tissue, blood and stool samples have been collected from over 600 subjects that have been linked to detailed longitudinal clinical metadata. The pilot data and publications generated by the GI Biobank over the previous funding period [19-25], contributed to our ability to successfully compete for a collaborative NCI P20 planning grant award entitled “Partnership to study racial/ethnic differences in GI cancer biology”. This planning grant supports a collaborative program between two SUNY medical campuses (Stony Brook Medicine and Downstate Medical Center) and the NCI-designated Cancer Center at Cold Spring Harbor Laboratories to evaluate biological and genetic differences in gastrointestinal cancers and to provide cancer health disparities research. This grant includes two collaborative pilot research programs, which will employ state of the art genomic analysis to compare African American samples with Caucasian samples since it is well established that the incidence and mortality of colorectal and pancreatic cancers are significantly higher in African Americans than in any other racial ethnic group.

This P20 award is designed to facilitate subsequent submissions of applications for much larger awards. One of the larger awards is a collaborative P50 Specialized Programs of Research Excellence (SPOREs) in Human Cancer focusing on GI cancers. This award requires the following elements: an Administrative Core, a GI Biobank core, 4 clinical translational projects, a developmental research program, and a research career development program. To assemble a competitive application for a GI SPORE, we will need to develop at least two more clinical translational projects that interact with the current projects we are developing through the P20 on racial/ethnic differences in colon and pancreatic cancer. Type 2 diabetes has been associated with increased risk of colorectal and pancreatic cancers. The increased prevalence of Type 2 diabetes in African Americans could contribute at least in part to the increased incidence and mortality of colorectal and pancreatic cancers in African Americans. Our hope is that development of clinical translational projects investigating the link between diabetes and GI cancers in **Aim 1**, may provide further insights on modifications in lifestyle or medications that reduce the risk of developing GI cancers. It may also determine whether patients with diabetes should receive more aggressive colonoscopic screening for prevention and early detection of colon cancer.

We have pioneered taking an integrative approach towards analyzing how inflammatory bowel disease genetic risk alleles and disease phenotype affect human intestinal-microbial interactions [8, 9, 16, 26]. Fecal microbial transplant (FMT) from health donors, has emerged as an effective (~90%) intervention for preventing further recurrence of *Clostridia difficile* infections [18]. Dr. Anupama Chawla, Associate Professor of Pediatrics and Chief of Pediatric Gastroenterology has initiated a phase 1 open label protocol to perform FMT in patients with recurrent *C. difficile* infections and/or ulcerative colitis, one of the two major inflammatory bowel diseases phenotype. The GI Biobank has supported the collection and processing of stool samples from the healthy donor and the recipients participating in this study. In our preliminary studies we have noted depletion of *F. prausnitzii* levels in patients with recurrent *C. difficile* colitis compared to healthy donors, which is restored post-transplant. Depletion of *F. prausnitzii* is a reproducible finding in patients with Crohn's disease, particularly those with disease affecting the distal small intestine or ileum [7-15]. Dr. Chawla plans to expand the study protocol to include patients with Crohn's disease. We anticipate that analysis microbial composition and function will address fundamental questions in microbiome research, such as 1.) whether alterations in the microbiome can be reversed, 2.) whether reversal of microbiome alterations can be linked to clinical improvement.

### Innovation

The key innovation is that the GI Biobank collects samples and clinical data in a project directed manner that involves clinicians in the frontlines of caring for patients with GI disorders at the outset in the design and execution of the clinical translational projects and in co-mentoring trainees (undergraduates, graduate students, medical students, residents, fellows, etc.). The organization of the sample and data collection efforts is modeled along the clinical service line responsible for caring for patients with GI cancer and inflammatory bowel diseases. In this way we can identify and obtain consent of potential subjects scheduled for surgery or endoscopic

procedures for clinical care and ensure that the GI Biobank staff are present to collect and rapidly transport the surgical resection and endoscopic biopsy samples so as to preserve RNA integrity. The clinicians also play a key role in phenotyping the subjects recruited for donation of research samples, and in determining the relevant clinical endpoints. Thus the clinicians are major stakeholders in the GI Biobank and participate in the decision on the distribution of patient samples to various projects. This has ensured high levels of recruitment of patients to donate to the GI Biobank (>90%).

The GI Biobank's consent includes **permission to carry out research genomic studies, including whole human genome sequencing studies**, on the frozen tissues and FFPE samples. The generation of preliminary RNA-Seq, high resolution methylation profiling data supported by Simon's Foundation Note that going forward, more stringent regulations are being put into place for genomic studies, which are anticipated to further restrict use of archived FFPE pathological samples without patient, or if the patient is deceased – family consent. Investigators requesting use of the samples are encouraged to partner with clinicians and must agree to allow data generated from the GI Biobank samples to be placed on an integrative biomedical informatics platform. The resulting accumulation of data will enrich any subsequent research projects using samples from the same subjects. This approach is similar to the approach that has been taken for use of data and samples through SFARI supported collections for autism research..

To facilitate the exchange of information and ideas, and to evaluate new projects. the GI Biobank has hosted a monthly GI research meeting that is video-streamed to SUY Downstate and CSHL. At these meetings, works in progress for projects utilizing GI Biobank samples have been presented and discussed among the participants at the three institutions. Furthermore investigators requesting GI Biobank samples are asked to present their proposed project in these meetings to obtain feedback from the clinicians and other research investigators, prior to making decisions on allocation of patient samples archived within the GI Biobank.

The GI Biobank has primarily supported observational studies over the past 5 years. **Aim 2** represents a departure from this approach in supporting an interventional study to explore the effect of fecal microbial transplant (FMT) of healthy donor stool on the microbiome patients with *C. difficile* colitis and/or inflammatory bowel diseases. This intervention has been proven to prevent further recurrence of *C. difficile* in patients with recurrent *C.difficile* with or without inflammatory bowel diseases. In **Aim 2**, we propose to use state of the art metagenomic and metatranscriptomic tools to characterize changes in microbial composition and function between IBD and healthy subjects as well as changes in the IBD subjects before and after FMT.

## Approach

### Aim 1. The effect of diabetes mellitus on colonic neoplasia.

Diabetes mellitus, particularly Type 2 diabetes mellitus, has been associated with an increased risk (~1.3-.14) of colorectal cancer in multiple studies [1-4]. With the support of the Simons Foundation over the past five years, a major focus of the GI Biobank has been to recruit all patients undergoing colon rectal surgery at Stony Brook University Hospital to donate intestinal surgical waste tissues (e.g. tissues not required for clinical diagnosis that would be otherwise discarded), blood, stool, permission to access archived formalin fixed paraffin embedded (FFPE) patient samples of tissue within the Department of Pathology for future genomic studies, and permission to collect longitudinal clinical metadata over the patients' lifetime.

Rigorous curation of the clinical metadata is critical for interpreting genomic and other data generated from patient samples. Thus far, the clinical metadata has included data on age, gender, smoking,

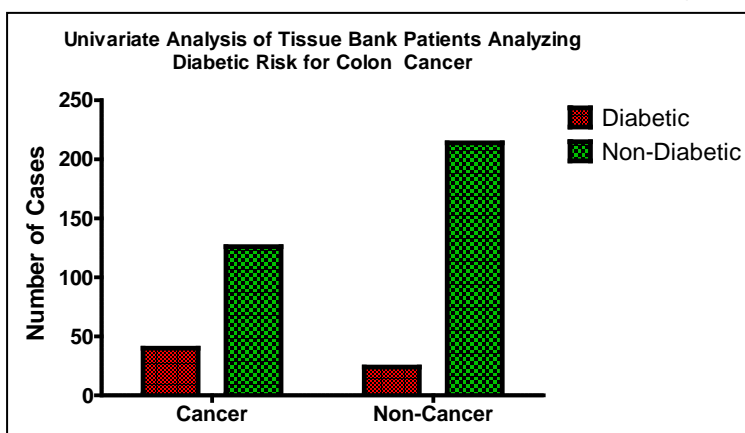


Fig. 1. Prevalence of diabetes in subjects with colon cancer compared to subjects without colon cancer in the Stony Brook GI Biobank.

diabetes, obesity, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), and personal and family history of colonic neoplasia, which have previously been identified as risk factors for colonic neoplasia, as well as medical insurance status, which is a measure of access to health care [20]. Accurate curation of the clinical metadata requires manual curation of the electronic medical records, and is thus highly labor intensive. For example we discovered that the diagnosis of diabetes mellitus could not be extracted from the problem list alone, but required careful review of the clinic notes and medications. In reviewing the 410 subjects who have donated colonic tissue samples from surgical resections, we noted that one fourth (40 of 166) subjects who underwent colorectal surgery for colon cancer in the GI Biobank (2010-2015) were diabetic, whereas one tenth (24 of 234) subjects who underwent colorectal surgery for non cancer indications were diabetic. Thus, the observations recorded in our GI Biobank over the past five years support the observation that there is a positive association between diabetes mellitus and colon cancer.

Colorectal cancer develops via a series of molecular and genomic changes in the adenoma-carcinoma sequence model from the 1.) normal epithelium, to 2.) early small adenomatous polyp, to 3.) larger advanced adenomatous polyp, to 3.) adenocarcinoma. A central question is whether diabetes mellitus stimulates the initial formation of adenomas, the conversion of early adenomas to advanced adenomas, or the transition from adenoma to carcinoma. There is conflicting evidence as to whether there is an increased prevalence of adenomas among patients with diabetes mellitus compared to those without [27-32]. To complicate the analysis, there is also evidence that the drugs used to treat diabetes mellitus have different effects on the risk of adenomas and/or carcinoma. Insulin has been associated with an increased risk of colonic neoplasia (adenoma and carcinoma) whereas metformin, which does not act by increasing insulin secretion, is associated with a reduced risk [34-36]. The GI Biobank also supported a retrospective analysis of colonoscopies performed at SBUH by collecting the same clinical metadata collected for our prospective collection of patients undergoing surgical resection at SBUH since 2010. The original rationale for the study was to examine the impact of a CDC funded project, Project SCOPE, to provide screening colonoscopies to underinsured patients in "Suffolk County New York [20]. The primary conclusion of this study was that Project SCOPE significantly boosted completion of screening colonoscopies in the Hispanic minority population in Suffolk County. In this study we also analyzed the factors associated with detection of colonic adenomas and detected no association between diabetes mellitus and adenomas. In this study, however, adenomas were not differentiated between early (size <1 cm with no villous or dysplastic features) and advanced adenomas (size  $\geq 1$  cm or with villous or with dysplastic features). So we were not able to address whether diabetes mellitus was associated with advanced adenomas. We also did not examine the effect of diabetes medications, which could serve as potential confounders in the analysis.

Potential mechanisms by which diabetes mellitus influences the neoplastic process include 1.) hyperglycemia; 2.) hyperinsulinemia, 3.) chronic inflammation [2]. Obesity has also been associated with colon cancer and to a lesser extent with colonic adenomas [37]. While by definition hyperglycemia is associated with diabetes mellitus, both insulin resistance and chronic inflammation have been associated with obesity and the metabolic syndrome [38].

**We propose to expand our GI Biobanking efforts to support clinical translational pilot projects to address the effect of diabetes mellitus on colonic neoplasia over the next funding period by:**

- A. *Expanding our retrospective collection of clinical metadata to more extensively phenotype with respect to covariates related to diabetes mellitus.***
- B. *Expanding our prospective GI Biobank recruitment to all patients undergoing initial screening colonoscopies for colon cancer for donation of research rectal tissue biopsies, blood and stool.***

1A. *Expanding our retrospective collection of clinical metadata to more extensively phenotype with respect to covariates related to diabetes mellitus.* In our current database, we simply captured whether patients carried the diagnosis of diabetes mellitus by reviewing the medical record. This effort was carried out in collaboration with Dr. Igor Kravets, Assistant Professor of Medicine in the Division of Endocrinology. Dr. Igor Kravets was the PI for a Department of Medicine Seed award to explore whether he could detect differential gene expression in colon cancers resected from patients with diabetes mellitus compared to patients without diabetes mellitus. He

is currently in the process of generating preliminary RNA-Seq data at the New York Genome Center from 12 subjects with type II diabetes mellitus and 12 without diabetes mellitus that are matched for BMI, age, and anatomic location of the cancer that had donated tissues to the GI Biobank.

*In order to test the hypothesis that hyperglycemia associated with poor diabetes mellitus control will be positively associated with the presence of advanced adenomas (size >10 mm, villous elements, dysplasia) in patients undergoing initial screening colonoscopies*, we will need to more extensively phenotype the patient with diabetes mellitus. This will be carried out initially retrospectively for both the colon surgical resection database and the colonoscopy database [20] maintained by the GI Biobank staff. The primary objective of retrospective phenotyping is to assess hyperglycemia or diabetic control by retrospectively reviewing FBS and Hemoglobin A1c levels in the diabetic patients. However given data suggesting that diabetes medications, particularly insulin and metformin, may serve as confounders, it is critical that subjects be more extensively phenotyped with respect to these medications. Finally, to address where diabetes mellitus impacts on the adenoma-carcinoma sequence, we will need to collect more detailed information on phenotyping adenomas as early vs. advanced. IN summary, we propose to expand phenotyping of diabetic patients by collecting the following additional information.

1. Hyperglycemia data
  - a. Fasting blood sugar (point of care day of colonoscopy)
  - b. Hemoglobin A1c (averaged over year pre colonoscopy)
2. Diabetes medications at the time of colonoscopy
  - a. Insulin
  - b. Sulfonylureas/meglitinides (insulin secretagogues)
  - c. Biguanides (metformin)
  - d. Thiazolidinediones
  - e. Incretin based therapies (Dipeptidyl peptidase-4 DPP-4 inhibitors (Januvia) and Glucagon-like peptide GLP-1 receptor agonists
  - f. Alpha glucosidase inhibitor (acarbose)
3. Adenoma pathology
  - a. Size
  - b. Presence of villous features
  - c. Presence of dysplasia
  - d. Location (proximal or distal to splenic flexure).

*1B. Expanding our prospective GI Biobank recruitment to all patients undergoing initial screening colonoscopies for colon cancer for donation of research rectal tissue biopsies, blood and stool.*

Although it is recommended that diabetic patients should routinely be monitored with respect to their HgbA1c levels, it is clear from our preliminary retrospective review (se 1A) that physician adherence to this recommendation is far from uniform. For this reason the GI Biobank proposes to initiate prospective recruitment all patients undergoing initial screening colonoscopy (~1200/year) to donate research endoscopic biopsies of the rectum, blood, stool, access to FFPE samples archived in the Pathology Department for future genomic studies, and longitudinal clinical information, similar to the recruitment currently taking place for all patients undergoing surgical resection of the colon. This collection effort is designed to support a pilot clinical translational study led by Dr. Joshua Miller, Assistant Professor of Medicine in the Division of Gastroenterology in collaboration with Dr. Igor Kravets (see above), Dr. Jonathan Buscaglia, Associate Professor of Medicine, Clinical Chief of Gastroenterology and Hepatology, Dr. Juan Carlos Bucobo, Assistant Professor of Medicine, Director of SBUH Endoscopy Unit, and Dr. Chris Lascarides, Associate Professor of Medicine, Director of Screening Colonoscopy Services and Outpatient Gastroenterology Services. The blood and research biopsy samples will be used to generate data on 1.) hyperglycemia, 2.) hyperinsulinemia and 3.) chronic inflammation in the following manner:

1. Hyperglycemia data

- a. Fasting blood sugar (blood)
  - b. Hemoglobin A1c (blood)
2. Hyperinsulinemia (insulin resistance)
    - a. Fasting insulin levels to calculate HOMA-IR = (fasting serum insulin (μU/ml) × fasting plasma glucose (mmol l-1)/22.5 (blood)
3. Chronic inflammation
    - a. Circulating cytokines and adipokines, e.g. IL-6 (blood) [39,40]
    - b. Rectal tissue gene expression of cytokines (tissue) [39]

In addition the archived blood, frozen tissue, FFPE samples, and stool can be used to support future genomic and metagenomics studies that are linked to extensive clinical data relating to diabetes mellitus, obesity and insulin resistance.

#### *Expected Results/Future Plans.*

In our retrospective analysis (2010-2015), we hope to demonstrate an association between poor diabetic glycemic control and advanced adenomas. To complete the retrospective analysis we have recruited in addition to the GI Biobank staff a cadre of medical students, medical residents and GI fellows to manually curate the necessary data. The statistical analysis will be supported by the GI Biobank staff.

The prospective analysis will represent a major expansion of patient recruitment for the GI Biobank with a goal of recruiting ~1000 subjects/year (80% of 1200 scheduled). Of the 1000 subjects recruited, we anticipate that 130 subjects (~13%) will carry the diagnosis of diabetes mellitus. (We may also identify additional patients as having diabetes mellitus because they had not been previously screened by their primary care physicians). Given that our overall adenoma detection rate is approximately 25%, which exceeds benchmark standard [41], we anticipate that ~250 subjects undergoing initial colon cancer screening each years will have at least one adenomatous polyp. Over three years, we hope to prospectively recruit 3000 subjects of whom ~ 390 subjects will be diabetic and ~750 subjects will have at least one adenomatous polyp.

The data and samples collected for **Aim 1** will be critical in developing translational epidemiologic project, which are required for a GI SPORE application. **The clinical data collected by the GI Biobank on potential covariates is not currently available on nationally maintained databases, such as the Cancer Genome Atlas (<http://cancergenome.nih.gov/>), which currently includes no information on diabetes mellitus, obesity, smoking etc.**

#### **Aim 2. Characterizing the effect of fecal microbial transplant on microbial composition and function in patients with recurrent *Clostridium difficile* infection and/or inflammatory bowel diseases.**

Fecal microbial transplant of healthy donor stool was initially conducted at Stony Brook University Hospital on two pediatric patients with ulcerative colitis in 2013 by one of the junior faculty members in the Division of Pediatric Gastroenterology. The rationale for conducting this procedure was based on small studies suggesting that pediatric patients with ulcerative colitis could improve clinically after the procedure [42]. This procedure was carried out without sampling the stools in either the donor or the recipient. Thus it was not possible to characterize the effect of the FMT on microbial composition and function in those two patients. However, shortly after these two procedures were carried out, the FDA determined that all fecal microbial transplants would require an investigational new drug (IND) application, other than fecal microbial transplants conducted for recurrent *Clostridia difficile* colitis. This is because of accumulated evidence that fecal microbial transplant is highly effective in preventing recurrence of *C. difficile*, which is the leading cause of infectious diarrhea in hospitalized patients and is associated with a high rate of recurrence (~20%) despite antibiotic therapy [43]. In many but not all cases, the initial infection occurs after antibiotic therapy. *C. difficile* infection can spread in a nosocomial manner between hospitalized patients. In addition, a high incidence of *C. difficile* infection (5% to 60%) has been reported in patients presenting with inflammatory bowel diseases flares [44].

In order to continue to offer FMT to patients with ulcerative colitis, Dr. Anupama Chawla, Associate Professor and Chief of Pediatric Gastroenterology successfully applied for an IND to treat patients with ulcerative colitis. Thus far, colonoscopic FMT of stool from healthy donors has been completed in 16 subjects with recurrent *C. difficile* infection and/or ulcerative colitis following an IRB-approved protocol led by Dr. Chawla. In order to characterize the effect of FMT on microbial composition and function, the GI Biobank has supported collection and banking of stool samples in the healthy donors at the time of the transplant and of stool samples collected from the recipients prior to the FMT, one week after the FMT and three months after the FMT. The Biobank has supported nucleic acid extraction of the stools. Preliminary quantitative PCR was performed using established universal and group specific primers to amplify portions of the 16S rRNA gene in order to quantitate total bacteria and the following bacterial subgroups: *Escherichia coli*, *Faecalibacterium prausnitzii*, *Clostridium coccoides-Eubacterium rectales*, and *Bacteroidetes* [45]. In these assays, the  $dCt = Ct$  (threshold cycle) total bacteria-Ct subgroup represents a  $\log_2$  transformation of the relative abundance of the subgroup/total bacteria.

The nine patients with recurrent *C. difficile* infections and who did not have inflammatory bowel diseases, were noted to have a marked pre-FMT reduction in the relative abundance of *F. prausnitzii* ( $dCt = -17.0 \pm 2.7$ ) compared to their healthy donors ( $dCt = -5.9 \pm 3.1$ ,  $p < 0.0001$ ). The relative abundance of *F. prausnitzii* was significantly increased in the recipients both at one week ( $dCt = -7.5 \pm 2.0$ ,  $n = 8$ ,  $p = 0.0002$ ) and three months ( $dCt = -7.5 \pm 1.5$ ,  $n = 4$ ,  $p = 0.019$ ). These patients also had a reduced relative abundance of *Bacteroidetes* ( $dCt = -15.7 \pm 3.2$ ) compared to their donors ( $dCt = -6.6 \pm 3.9$ ,  $n = 9$ ,  $p < 0.0001$ ). The relative abundance of *Bacteroidetes* was significantly increased in the recipients at one week ( $dCt = -7.2 \pm 5.3$ ,  $n = 8$ ,  $p = 0.0097$ ) but did not reach significance at 3 months ( $dCt = -11.4 \pm 3.3$ ,  $n = 4$ ,  $p = .11$ ). Differences in the relative abundances of other bacterial subgroups did not reach significance between the recipients and the healthy donors. All of the patients had no recurrence of *C. difficile* infections over one year post-FMT, with the exception of one patient who required interim surgery and antibiotic therapy for a chronic rectal fistula that was present at baseline.

The five ulcerative colitis patients who did not have *C. difficile* infections, were also noted to have a lower pre-FMT relative abundance of *F. prausnitzii* ( $dCt = -9.1 \pm 3.6$ ) compared to their donors ( $dCt = -4.7 \pm 1.5$ ,  $p = .0367$ ). Increases in the relative abundances of *F. prausnitzii* at one week ( $dCt = -4.6 \pm 2.9$ ,  $n = 5$ ,  $p = 0.075$ ) and three months ( $dCt = -4.7 \pm 1.9$ ,  $n = 4$ ,  $p = 0.15$ ) post-transplant did not reach significance compared to recipient pre-FMT levels. It should be pointed out that the decrease in *F. prausnitzii* relative abundance in the 5 UC patients was not as striking as that observed for the 9 patients with *C. difficile* infections. No significant differences were observed in the pre-FMT relative abundances of the other three bacterial subgroups compared to their healthy donors. In the UC patients, disease severity was assessed using the Mayo score [46]. The mean baseline Mayo score was  $4.6 \pm 3.4$  ( $n = 5$ ), and the three month post-FMT Mayo score was  $3.0 \pm 1.0$  ( $p = 0.87$ ) in the three patients who underwent follow up sigmoidoscopy.

The two remaining patients had both inflammatory bowel diseases (one with ulcerative colitis and one with ileal Crohn's disease) and recurrent *C. difficile* infections. Neither of these patients had recurrence of *C. difficile* over one year. In these two patients the mean pre-FMT relative abundance of *F. prausnitzii* ( $dCt = -18.2 \pm 1.0$ ) was lower than the mean value for their respective donors ( $dCt = -6.7 \pm 1.0$ ). Increases were observed in the relative abundances of *F. prausnitzii* at one week ( $dCt = -12 \pm 7$ ) and at three months ( $dCt = -2.4 \pm 0.3$ ).

We were particularly intrigued with the observation that FMT appeared to replete *F. prausnitzii* levels in the patients we have recruited thus far. This is because depletion of *F. prausnitzii* has been reproducibly found in Crohn's disease patients, particularly those with ileal disease [7-15].

**We propose to expand our GI Biobanking efforts to support clinical translational pilot projects to characterize the effect of fecal microbial transplant on microbial composition and function by:**

**A. Expanding recruitment of patients undergoing FMT to include patients with Crohn's disease, as well as continuing to recruit patients with recurrent *C. difficile* colitis and ulcerative colitis.**

**B. Characterizing the effect of FMT on microbial composition and function in patients with recurrent *C. difficile* infection and/or inflammatory bowel diseases.**

2A. Expanding recruitment of patients undergoing FMT to include patients with Crohn's disease, as well as continuing to recruit patients with recurrent *C. difficile* colitis and ulcerative colitis.

In contrast to the accumulated experience for FMT in patients with recurrent *C. difficile* colitis, it remains to be determined what the clinical efficacy will be for performing FMT in patients with either of the major phenotypes for inflammatory bowel diseases, ulcerative colitis or Crohn's disease [18,42, 47-55]. Dr. Chawla's rationale for conducting phase 1 open label trials rather than randomized trials is that patients would only be willing to participate in an open label trial. Healthy donors selected by the patients, rather than using a single donor source, are proposed in order to have sufficient power to compare the baseline pre-FMT recipient samples with the healthy donor samples. Our preliminary data indicate that the FMT can successfully restore depleted levels of *F. prausnitzii*. If depletion of *F. prausnitzii* contributes significantly to the pathogenesis of the disorder, we reason that restoration of *F. prausnitzii* may provide clinical benefit to the patient. Our rationale for expanding Dr. Chawla's study to include patients with Crohn's disease in addition to patients with ulcerative colitis, is because depletion of *F. prausnitzii* levels has been widely reported in patients with Crohn's disease.

We plan to submit a new IND application to perform FMT in patients with Crohn's disease. Because patients with Crohn's disease have small intestinal disease, we propose to administer the donor stool into the duodenum by duodenoscopy rather than by colonoscopy.

Stony Brook University Hospital is currently the only medical center on Long Island, NY that offers FMT for recurrent *C. difficile* and/or ulcerative colitis. We perform the procedure only by study protocol. We have received multiple inquiries from Crohn's disease patients about FMT, and anticipate no difficulty in recruiting approximately 30 patients each year with recurrent *C. difficile* infection and/or inflammatory bowel diseases.

2B. Characterizing the effect of FMT on microbial composition and function in patients with recurrent *C. difficile* infection and/or inflammatory bowel diseases.

### 2B.1 16S rRNA Sequencing

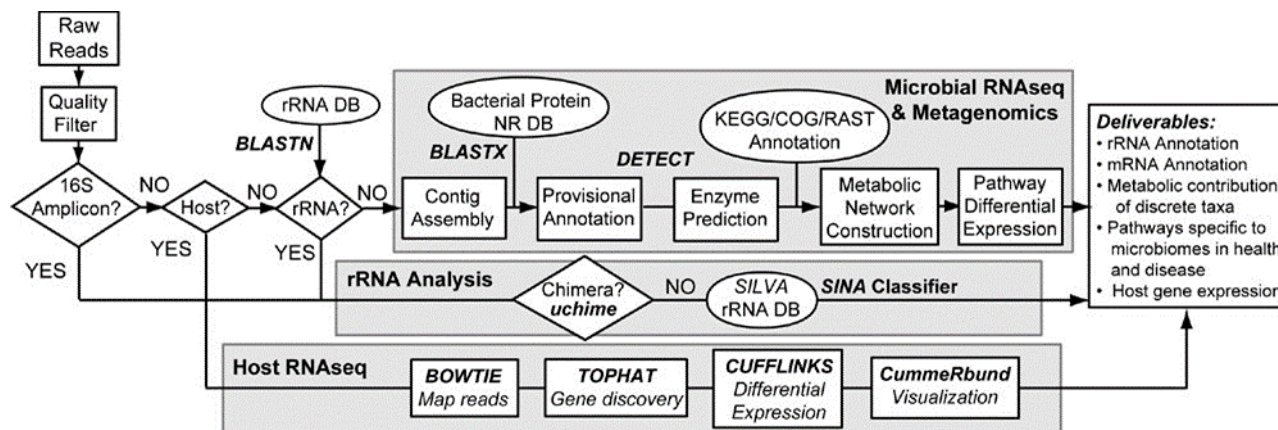


Fig. 2. Unified software platform for analysis of 16S amplicons sequences, microbial metagenomics and meta-RNAseq

In order to further characterize alterations in microbial composition between the baseline recipient stools and the healthy donor stools, and to characterize the effect of FMT on recipient fecal microbial composition, we propose to generate 16S rRNA sequence data on all the stool samples collected in the study. We have previously used 454 pyrosequencing of the V3V5 region (550 bp) [10,11], however this technology is no longer being supported. Illumina sequencing technology is rapidly evolving to generate longer sequence reads at lower cost [45, 56]. Our analytic pipeline will use the computational tools and quality control criteria that are generally accepted as standards of the microbiome community at the outset of the study. 16S rRNA amplicon processing is embedded within a larger software pipeline for metagenomic/metatranscriptomic network analysis (see Fig.

2). This pipeline consists of both novel analytic tools we have developed (e.g., DETECT) and third-party software programs linked together with python scripts that exploit multi-core computer processors [57]. For analysis of Illumina platform sequencing, we demand that both paired end reads contain 100% matches to barcode and 16S primer sequences; barcodes differ from one another by >2 bases so miss-classification requires at least two sequencing errors. Following de-multiplexing, paired-end reads are assembled into contigs using phrap and reads that do not assemble are discarded [58, 59]. 5' and 3' ends of assembled sequences are trimmed over a moving window of 5 nucleotides until average quality meets or exceeds 20. Trimmed sequences are discarded if they 1) contain more than 1 ambiguous base; 2) have average quality scores less than 25; or 3) are shorter than 400 nt. Potential chimeras are identified with Uchime (usearch6.0.203\_i86linux32) [60] using the Schloss Silva reference sequences and removed from subsequent analyses [61]. The remaining sequences are aligned and classified with SINA (version 1.2.11) using the 418,497 bacterial sequences in Silva version 115NR99 as reference configured to yield the Silva taxonomy [62]. Any sequence that is unclassified by SINA, such as an aberrantly amplified human DNA sequence, will be excluded from further analysis. Similar rRNA sequences are grouped into operational taxonomic units (OTUs) based on Silva classifications. Ecological indices [63] of richness (e.g. Sobs, Schao), diversity (e.g., Shannon's diversity [Ho]), evenness (Shannon's evenness [Ho/Hmax]), and coverage (e.g., Good's index) are calculated with the software package Explicit [64] through 1000 bootstrap replicates and rarefaction analysis. All libraries will be sequenced to a Good's coverage of >97% to ensure accurate estimation of alpha-diversity. Beta diversity will be calculated using the adonis function in the R vegan package [65]. This function uses a non-parametric multivariate analysis of variance test (PERMANOVA) [66], and will be applied using Bray-Curtis, Jaccard and Morisita-Horn indices as distance measurements [67]. Comparisons of recipient stools, before and after FMT, and the healthy donor stools will be conducted with 1.) raw sequences (prior to binning into OTUs) and 2.) after binning into OTUs, as previously described [54, 68]

## 2B.2 Metatranscriptomic RNA-Seq and metagenomic shotgun gDNA sequencing.

In order to further characterize alterations in microbial function between the baseline recipient stools and the healthy donor stools, and to characterize the effect of FMT on recipient fecal microbial composition, we propose to generate metagenomic and metatranscriptomic sequences on a subset of stool samples. Microbial mRNA expression potentially is a better surrogate for community function in a particular niche than is genomic DNA (gDNA) sequencing, the latter of which indicates only the potential for gene expression. Furthermore deep shot-gun sequencing of RNA can potentially uncover non-bacterial etiological agents such as viruses, archaea, or microbial eukaryotes that would be missed by bacterial 16S sequencing. We propose to conduct 150 bp single end Illumina RNA-sequencing to a depth of 20,000,000 on selected stool RNA samples that have been depleted of bacterial rRNA and analyzed as previously described [69,70].

Although bacterial metatranscriptomics provides information on which bacterial genes are expressed at the mRNA level, the protocols for producing high-quality genomic DNA (gDNA) are more robust than for bacterial metatranscriptomics. gDNA metagenomics sequencing also is less affected by representational biases that would arise if housekeeping mRNA transcripts dominate a community (re-sequencing very highly expressed housekeeping genes, such as mRNAs encoding ribosomal proteins is uninformative and may obscure the detection of critical mRNAs of low abundance). Furthermore, sequencing DNA rather than mRNA may uncover genomic elements (promoters, transposable elements, CRISPR elements) that are not expressed as mRNA, yet have functional significance in a microbiome. Finally gDNA sequencing is less subject to bias introduced by primer selection for 16S rRNA sequencing. Functional/phylogenetic annotations of all reads will be made using the MGRAST server [71].

## *Expected Results/Future Plans.*

We hope to recruit 30 patients a year for FMT with either recurrent *C. difficile* and or inflammatory bowel diseases. Based on our preliminary qPCR results, we predict that 16S rRNA sequencing data will demonstrate that there is reduced abundance of *F. prausnitzii* in patients with recurrent *C. difficile* and with ileal Crohn's disease pre-FMT that will be restored after FMT. We hope to characterize alterations in other bacterial taxa.

This award will support metatranscriptomic and metagenomics sequencing of selected samples that will be serve as critical preliminary data for an RO1 we propose to submit in the next year and hope to successfully compete for funding in the next two years.

### **Protection of Human Subjects.**

The GI Biobank has obtained approval from the SBU Institutional Review Board (IRB# to prospectively consent and archive tissues, blood and stool collected from surgical and endoscopic procedures that have been scheduled for clinical care. Inclusion criteria: Subjects  $\geq 18$  years able and willing to give informed consent, Minor subjects  $<18$  and  $>7$  years who are willing to provide assent and whose parents are both willing to give consent. Minors are reconsented as an adult once they reach the age of 18. Exclusion criteria: Patients  $\geq 18$  who are unwilling or unable to give informed consent. Patients  $< 7$  years. Patients  $\geq 7$  years and  $< 18$  years who are unwilling to give assent or whose parents are unwilling to give informed consent. Prisoners. The GI Biobank and the SBU DDR TPF collect blood, saliva, stool, endoscopic biopsies and surgical waste and access to existing clinical pathology (FFPE blocks) specimens using a common one-time consent template that allows for longitudinal follow-up and collection of serial samples, if the subject consents at the time of the subsequent procedure or visit. Both facilities are covered by a NIDDK issued Certificate of Confidentiality. The clinical information, tissues and bodily fluids are stripped of all identifying information and linked by patient and sample codes prior to storing the information on servers maintained by each facility, with appropriate fire wall protection.



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## **FACILITIES, EXISTING EQUIPMENT AND OTHER RESOURCES**

### **Stony Brook University:**

#### **Laboratory:**

**SBU Digestive Diseases Research Tissue Procurement Facility.** This facility is located within SBU GI Division Research space and is directed by Dr. Li. It follows the same standard operating procedures employed in the WUSTL DDRCC GI Biobank and has an ongoing collection of clinical data and specimens collected from >600 patients with gastrointestinal diseases. It is equipped with -80 freezers for storage of the tissue samples and their downstream products (RNA and DNA) as well as biohazard hoods, microfuges, Nanodrop 1000, Eppendorf Realplex, Agilent 2100 Bioanalyzer.

**Center of Excellence in Wireless and Information Technology (CEWIT).** Dr. Li has a dry laboratory within the Center of Excellence in Wireless and Information Technology (CEWIT) at Stony Brook University. The Center is located in Stony Brook University Research and Development Park and houses faculty from multiple departments including Applied Mathematics, Medicine, Radiology, Computer Science. These dry laboratories house graduate students in the Department of Applied Mathematics and Statistics, who are focused on developing novel computational tools for integrating multidimensional datasets.

**Clinical:** Stony Brook University Medical Center is the only major academic medical center in Long Island and is a tertiary referral center for east Long Island.

#### **Animal: N/A**

**Computer:** The laboratory is equipped with multiple personal computers and workstations for analysis of multidimensional datasets. The proposed server will be installed on the secured segment of CEWIT network behind the CEWIT firewall. It will be configured for only allowed computers from other institutions to access and deposit data. For example, server software using Secure File Transfer Protocol (SFTP) will be installed and configured on this proposed server. The SFTP server is platform independent and has the capability to resume interrupted transfers. The SFTP server will allow remote computers with SFTP client from other institutions to transmit data securely. CEWIT IT staff will work closely with IT staff from other institutions if necessary to automate secure data transmission to CEWIT SFTP server if the data transfer becomes a burden to researchers as the amount of data increases dramatically during the tenure of this proposed project. The research data on this SFTP server will be backed up periodically to CEWIT storage cloud. In addition, there are three High-Performance Computing (HPC) clusters in CEWIT. They are (1) a custom-built 470-processor Linux Cluster, Seawulf Cluster, which uses 3.4GHz Intel Pentium IV Xeon CPUs interconnected with Gigabit Ethernet, with a total of 20TB of high speed disk space; (2) a custom built 450-processor Galaxy parallel supercomputer, recently upgraded to 3.2GHz Intel Pentium IV Xeon CPUs interconnected with Gigabit Ethernet, with a total of 4TB of high speed disk space; (3) a 228-processor Rocks Clusters with 113 computing nodes interconnected with Gigabit Ethernet and a 100TB storage clusters with 35TB disk backup clusters. The IBM Blue Gene supercomputer, named New York Blue and located at Brookhaven Lab, is the world's fastest supercomputer for general users and is expected to rank among the top ten fastest computers in the world. We have internet/network access through the SBU network and also the CEWIT network. The CEWIT network, one of the best in US academia, will host the proposed project internet website.

**Office:** Dr. Li has an office in SBU GI Division and at CEWIT.

**Other:** see above.

### **University of Colorado-Denver**

**Laboratory:** Dr. Frank's laboratory is located in the Research Complex II building at the University of Colorado Denver AMC. The Frank laboratory, along with core facilities available through the Division of Infectious Diseases, provides all of the equipment necessary for the proposed analyses. The lab occupies 400+ sq. ft. of near-new facilities in a modern clinical and molecular biology research building on the UC Denver Anschutz

Medical Campus. This research space is designed to provide optimal BSL2+ safety conditions for working with infectious human pathogens, with limited access and negative air pressure. We have designated areas for cell culture, antibody work (ELISA and purification), bacteriology, immunohistochemistry, and molecular biology procedures, which include four 6 foot Class II biosafety cabinets and two water-jacketed CO2 incubators for cell culture, and a Molecular Devices Elisa reader. Other equipment includes thermocyclers (e.g., ABI3700 and BioRad QPCR platforms), bead-beaters, Qubit fluorimeter, gel imagers, NanoDrop spectrophotometer, fluorescence microscopy, electrophoresis equipment, centrifuges, two positive-pressure PCR hoods, -20°C and -80°C freezers, liquid nitrogen dewar flasks, Coulter ZBI particle counter with Channelyzer size analyzer, an American Optical direct microscope for hemacytometer cell counting and cell morphology, a Zeiss inverted microscope for cell culture examination, a Zeiss Steroscope for counting ELISPOTs and Immuno-diffusion plates, two Bio-Rad FPLC Econosystems for Immunoglobulin purification, and a Molecular Devices VERSAmax ELISA plate reader. Other support facilities include autoclaves, dishwashing facilities, etc.

The Frank laboratory operates the ID Division's Illumina MiSeq Personal Sequencer and have performed >60 runs on this platform. We routinely generate 5-20x106 paired end reads (600 nt) per instrument run from 16S amplicons, genomes, or metagenomes. The Frank lab is equipped with 32-core and 24-core Xeon servers with 1.7 terabytes of RAM, 40 terabytes of failure resistant (RAID6) disk space and NVIDIA compute cards for acceleration of some algorithms (GPGPU). This hardware is capable of processing typical microbiome sequence data sets from Illumina MiSeq in a few hours.

**Clinical:** N/A

**Animal:** N/A

**Computer:** The lab is well equipped with MacIntosh and Linux computers appropriate for the project.

**Office:** Dr. Frank's office occupies 200 sq. ft. and is adjacent to his laboratory.

**Other**



# Stony Brook Research

## Stony Brook University Institutional Review Board (IRB)

DATE: March 23, 2015

TO: Ellen Li, M.D.-Ph.D

FROM: Stony Brook University IRB (CORIHS B)

SUBMISSION TYPE: Amendment/Modification

STUDY TITLE: [163184-24] Stony Brook Digestive Diseases Research  
Tissue Procurement Facility

CORIHS#: 2014-1058-FAR

ACTION: APPROVED

MEETING DATE (IF FULL REVIEW):

SUBMISSION APPROVAL DATE: March 23, 2015

PROJECT EXPIRATION DATE: January 21, 2016

REVIEW TYPE: Expedited

Amendment #9 per PI memo dated 02/12/15: Consent and Assent updated to include information for the subject that the collected tissue samples may be stored at the SBU BioBank and/or at the DDR TPF facility.

Thank you for your submission of Amendment/Modification materials for this research study. Stony Brook University IRB (CORIHS B) (FWA #00000125) has APPROVED your submission.

All research must be conducted in accordance with this approved submission. Any modifications to the study as approved must be reviewed and approved by CORIHS prior to initiation.

If this activity has components that require approval from additional compliance committees (e.g., IACUC, IRB, IBC, SCRO, COI) it is your responsibility to not commence with the study until these approvals have been secured as well.

### Please note:

- Consent forms signed by subjects in this study must be kept by the investigator for 6 (six) years from study termination, or indefinitely (if so indicated in the consent form).
- Inclusion of minors in this study is acceptable in accordance with 45 CFR 46.404
- Parental permission and minor assent is obtained in accordance with 45 CFR 46.408. Minor assent is also obtained in accordance with SBU Assent Policy, Category 1.

You are reminded that you must apply for, undergo review, and be granted continued approval for this study before January 21, 2016 in order to be able to conduct your study in an uninterrupted manner. If you do not receive approval before this date, you must cease and desist all research involving human subjects, their tissue and their data until such time as approval is granted.

Where obtaining informed consent/permission/assent is required as a condition of approval, be sure to assess subject capacity in every case, and continue to monitor the subject's willingness to be in the study throughout his/her duration of participation. Only use current CORIHS-stamped forms in the consent process. Each subject must receive a copy of his/her signed consent/permission/assent document.

Unanticipated problems (including serious adverse events) must be reported to this office in accordance with SBU Policy at: <http://research.stonybrook.edu/human-subjects-standard-operating-procedures/unanticipated-problems-involving-risks-subjects-or>.

Any complaints or issues of non-compliance must be immediately reported to this office. If you have any questions or comments about this correspondence, please contact:

Office of Research Compliance  
Division of Human Subject Protections  
Stony Brook University  
Stony Brook, NY 11794-3368.  
Phone: 631-632-9036  
Fax: 631-632-9839

**Please include your study title and CORIHS # in all correspondence with this office.**

We are interested in receiving feedback regarding your experience with the Office of Research Compliance, SBU's IRBs (CORIHS), or any other aspect of our Human Research Protection Program. Please feel free to e-mail Judy Matuk, Assistant Vice President for Research Compliance, at [judy.matuk@stonybrook.edu](mailto:judy.matuk@stonybrook.edu), or if you'd like to submit feedback anonymously, you may do so at <http://www.tellmyirb.com>, choose the option 'Report a Problem', type in 'Stony Brook' as the site, click the radio button on the following screen, and then provide feedback!