Project Information

5R01CA188654-05

DESCRIPTION | DETAILS | RESULTS | HISTORY | SUBPROJECTS

Project Number: 5R01CA188654-05
Title: MR-HIFU INDUCED DRUG DELIVERY FOR PANCREATIC CANCER TREATMENT

Contact PI / Project Leader: LEE, DONGHOON
Awardee Organization: UNIVERSITY OF WASHINGTON

Abstract Text:

DESCRIPTION (provided by applicant): Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States. Surgical resection offers the only chance of cure with an about 20% 5-year survival but more than 80% of patients present with advanced unresectable disease. The overall 5-year survival rate for all types of pancreatic cancer is less than 5%. Pancreatic tumor therapy has been ineffective partly because pancreatic tumors have a dense stroma inhibiting penetration of chemotherapeutic drugs into the tumor. High intensity focused ultrasound (HIFU) can be used to induce targeted hyperthermia leading to increased perfusion potentially enhancing targeted drug delivery (TDD) to pancreatic tumors with deficient vasculature. In addition, pulsed HIFU has potential to mechanically disrupt stroma resulting in increased permeability of the dense stroma in pancreatic tumors. One major challenge with the HIFU-enhanced TDD is the absence of noninvasively assessing treatment efficacy following the HIFU application. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have been widely used as key noninvasive methodologies for clinical tumor diagnosis and treatment follow-up due to their good spatial resolution compared to other imaging modalities. However, with respect to pancreatic tumors, conventional MRI has been used for qualitative detection of pathologic regions for diagnosis and treatment follow-up with limited resolution and inability of quantification for preclinical studies using mouse models. Therefore, more effective magnetic resonance (MR) biomarkers with high resolution are needed to monitor treatment responses of tumors treated with HIFU in tumor bearing mice. We hypothesize 1) HIFU induced hyperthermia will enhance TDD and pancreatic tumor cell death in a targeted region and quantitative MR will enable assessment of the treatment 2) pulsed HIFU will disrupt stromal layers in pancreatic tumor and MRI/MRS will assess the process of stromal layer disruption. The overall goal of this study is 1) to generate effective HIFU induced hyperthermia for targeted chemotherapeutic drug delivery for a pancreatic tumor mouse model (KPC) that closely resembles human pancreatic cancer and 2) to accurately monitor both mild hyperthermia and responses to pancreatic tumor treatments based on the HIFU-enhanced TDD using noninvasive and quantitative MRI and MRS methods at high resolution. To accomplish the study goal we propose three specific aims: 1) to assess pancreatic tumor progression for the KPC mouse model with advanced MR methods, 2) to evaluate perfusion and degree of stromal layer disruption after HIFU and 3) to assess responses to chemotherapeutic treatments mediated by HIFU. The development of noninvasive MR biomarkers, pulsed HIFU method and effective KPC mouse model will be essential to advance the understanding of this deadly disease and has the potential to be used to assess promising therapies in pre- clinical and clinical trials.

Public Health Relevance Statement:

PUBLIC HEALTH RELEVANCE: Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States and the overall 5- year survival rate is less than 5%. The main goal of this study is to develop effective targeted drug delivery mediated by focused ultrasound for pancreatic tumor and to accurately monitor responses to pancreatic tumor treatments using noninvasive and quantitative magnetic resonance methods at high resolution. The successful completion of this project will be a major step toward the promising treatment approach for human patients who are suffering from the deadly disease.

Project Terms:

Accounting; Aftercare; anticancer research; base; Biological Markers; Calibration; Cancer Etiology; cancer therapy; Cell Death; Cessation of life; chemotherapeutic agent; chemotherapy; Clinical; Clinical Trials; cold temperature; contrast enhanced; Detection; Development; Diagnosis; Diffusion Magnetic Resonance Imaging; Disease; Drug Delivery Systems; Drug Targeting; Evaluation; Excision; Focused Ultrasound; Focused Ultrasound Therapy; follow-up; Gadolinium; gemcitabine; Genetic; Genetically Engineered Mouse; Goals; Human; Hyperthermia; imaging modality; in vivo; Induced Hyperthermia; Injections; Liposomes; Magnetic Resonance; Magnetic Resonance Imaging; Magnetic Resonance Spectroscopy; Malignant neoplasm of pancreas; Measurement; Mechanics; Mediating; Methodology; Methods; Modeling; Monitor; mouse model; Mus; Noise; Operative Surgical Procedures; pancreatic cancer cells; pancreatic cancer patients; Pancreatic Ductal Adenocarcinoma; pancreatic neoplasm; Pathologic; Patients; Penetration; Perfusion; Permeability; Pharmaceutical Preparations; Physiologic pulse; preclinical study; preclinical trial; Preparation; Process; public health relevance; radio frequency; Resectable; Resolution; response; Sampling; Signal Transduction; Survival Rate; System; therapeutic development; Treatment Efficacy; treatment response; tumor; tumor progression; Ultrasonography; United States; Unresectable

Contact PI Information:	Program Official Information:	Other PI Information:
Name: LEE, DONGHOON **Email**: Click to view contact PI email address **Title**:	**Name**: FARAHANI, KEYVAN **Email**: Click to view PO email address	Not Applicable

Organization:	Department / Educational Institution Type:	Congressional District:
Name: UNIVERSITY OF WASHINGTON **City**: SEATTLE Country: UNITED STATES (US)	RADIATION-DIAGNOSTIC/ONCOLOGY SCHOOLS OF MEDICINE	State Code: WA District: 07

Other Information:

FOA: PAR-13-185 DUNS Number: 605709469 CFDA Code: 394

FOA: PAR-13-185 **DUNS Number**: 605799469 **CFDA Code**: 394

Study Section: Special Emphasis Panel (ZRG1-SBIB-Z (58)R) **Project Start Date**: 12-AUG-2015 **Project End Date**: 31-JUL-2020

Fiscal Year: 2019 **Award Notice Date**: 1-JUL-2019 **Budget Start Date**: 1-AUG-2019 **Budget End Date**: 31-JUL-2020

Administering Institutes or Centers:

NATIONAL CANCER INSTITUTE

Project Funding Information for 2019:

Total Funding: $524,312 **Direct Costs:** $313,542 **Indirect Costs:** $210,770

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL CANCER INSTITUTE	$524,312

History:

Total project funding amount for **5** projects is **$2,600,851***

** Only NIH,CDC,and FDA funding data.*

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
5R01CA188654-05		MR-HIFU INDUCED DRUG DELIVERY FOR PANCREATIC CANCER TREATMENT	LEE, DONGHOON	UNIVERSITY OF WASHINGTON	2019	NCI	NCI	$524,312
5R01CA188654-04		MR-HIFU INDUCED DRUG DELIVERY FOR PANCREATIC CANCER TREATMENT	LEE, DONGHOON	UNIVERSITY OF WASHINGTON	2018	NCI	NCI	$519,459
5R01CA188654-03		MR-HIFU INDUCED DRUG DELIVERY FOR PANCREATIC CANCER TREATMENT	LEE, DONGHOON	UNIVERSITY OF WASHINGTON	2017	NCI	NCI	$495,976
5R01CA188654-02		MR-HIFU INDUCED DRUG DELIVERY FOR PANCREATIC CANCER TREATMENT	LEE, DONGHOON	UNIVERSITY OF WASHINGTON	2016	NCI	NCI	$502,708
1R01CA188654-01A1		MR-HIFU INDUCED DRUG DELIVERY FOR PANCREATIC CANCER TREATMENT	LEE, DONGHOON	UNIVERSITY OF WASHINGTON	2015	NCI	NCI	$558,396

Subprojects:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	FY Total Cost by IC
No Subprojects information available for 5R01CA188654-05							

Project Information

5R01CA154451-06

DESCRIPTION | DETAILS | RESULTS | HISTORY | SUBPROJECTS

Project Number: 5R01CA154451-06
Title: ULTRASOUND-ENHANCED DRUG PENETRATION FOR TREATMENT OF PANCREATIC CANCER

Contact PI / Project Leader: HWANG, JOO HA
Awardee Organization: UNIVERSITY OF WASHINGTON

Abstract Text:

PROJECT SUMMARY Pancreas cancer is the fourth leading cause of cancer mortality in the United States, with very few effective therapeutic options. The median survival rate for resectable tumors is only 2 years, and systemic chemotherapy with gemcitabine only offers a modest survival benefit. The main characteristic of pancreas tumors that makes chemotherapy treatment difficult is the extensive stromal desmoplasia, which decreases blood perfusion, increases the intratumoral pressure and impedes the delivery of chemotherapy. Disrupting the stromal barrier would both increase perfusion and permeabilize the tumor, enhancing penetration of chemotherapy. In our initial grant period we successfully demonstrated that mechanical disruption of the stroma using pulsed high intensity focused ultrasound (pHIFU)-induced cavitation resulted in enhanced penetration of doxorubicin by up to 4.5-fold. These results were obtained in an in vivo genetically engineered mouse model (KPC mouse) of pancreatic ductal adenocarcinoma, using an optimized ultrasound-guided pHIFU small animal treatment system. The KPC model, unlike xenograft or subcutaneous models, closely recapitulates the genetic mutations, clinical symptoms and histopathology found in human pancreatic cancer. These results are readily translatable to patient treatment. In this renewal application we propose to evaluate the tumor response and survival of KPC mice treated with pHIFU and systemic administration of gemcitabine. We will then develop a new ultrasound-guided pHIFU clinical system that incorporates Bubble Doppler imaging algorithms to enable monitoring of pHIFU therapy. The system will be designed, fabricated and characterized following FDA guidelines. The main paradigm shift compared to the small animal studies is the design of ultrasound transducers that produce less focused, lower frequency (sub-MHz) HIFU beams that affect larger tissue areas and may have a different physical mechanism of cavitation nucleation compared to high- frequency, highly focused transducers used previously. We hypothesize that this change will: 1) shorten treatment duration; 2) provide deeper penetration depth; 3) allow the use of lower pHIFU pressure amplitudes and therefore improve safety. The other major innovation of this proposal is the further development of a unique cavitation mapping technique, discovered by our group during the initial grant period and termed Bubble Doppler, which enables ultrasound-based monitoring of pHIFU therapy in real-time. We will complete preclinical evaluation of the feasibility and safety of pHIFU treatments using Bubble Doppler monitoring in porcine pancreas in a series of acute and short term survival studies. In parallel, a clinical trial using this therapy device will be designed. All relevant reports will be compiled to apply for an investigational device exemption (IDE) to US FDA to conduct a clinical trial in patients with pancreatic cancer.

Public Health Relevance Statement:

NARRATIVE Pancreas cancer is expected to become the second deadliest cancer in the United States by 2020. Current standard of care only offers a modest survival benefit due to extensive fibrous matrix, which impedes chemotherapy delivery. The proposed work will benefit public health by bringing to clinical translation the promising new technology of ultrasound-guided pulsed HIFU for enhancing the penetration of chemotherapeutic drugs into pancreatic tumors.

Project Terms:

Abdomen; Acute; Affect; Algorithms; Animal Model; Animals; Area; base; blood perfusion; Cancer Etiology; Characteristics; chemotherapy; Clinical; clinical application; clinical translation; Clinical Treatment; Clinical Trials; Conduct Clinical Trials; design; Desmoplastic; detector; Development; Devices; DNA Sequence Alteration; Doxorubicin; Elements; Family suidae; Focused Ultrasound Therapy; Frequencies; gemcitabine; Genetically Engineered Mouse; Grant; Guidelines; Hemorrhage; Histologic; Histopathology; Human; Image; image guided; imaging probe; improved; in vivo; Injury; innovation; Investigation; Knowledge; Link; Malignant neoplasm of pancreas; Malignant Neoplasms; Maps; Measurement; Mechanics; Modeling; Monitor; mortality; Mus; new technology; novel; Office Visits; Pancreas; pancreatic cancer model; pancreatic cancer patients; Pancreatic Ductal Adenocarcinoma; pancreatic neoplasm; Patients; Penetration; Perfusion; Pharmaceutical Preparations; Physiologic pulse; preclinical evaluation; pressure; Procedures; Protocols documentation; Public Health; Reporting; research clinical testing; Resectable; response; Safety; safety and feasibility; safety assessment; Series; standard of care; subcutaneous; Survival Rate; Symptoms; System; Techniques; Therapeutic; Time; Tissues; Transducers; Translating; Translational Research; treatment duration; Treatment Efficacy; Treatment Protocols; tumor; Ultrasonic Transducer; Ultrasonography; United States; Work; Xenograft procedure

Contact PI Information:	Program Official Information:	Other PI Information:
Name: HWANG, JOO HA **Email**: Click to view contact PI email address **Title**: ASSOCIATE PROFESSOR OF MEDICINE	**Name**: TANDON, PUSHPA **Email**: Click to view PO email address	Not Applicable

Organization:	Department / Educational Institution Type:	Congressional District:
Name: UNIVERSITY OF WASHINGTON **City**: SEATTLE Country: UNITED STATES (US)	INTERNAL MEDICINE/MEDICINE SCHOOLS OF MEDICINE	State Code: WA District: 07

Other Information:

FOA: PAR-16-044
Study Section: Special Emphasis Panel (ZRG1 SBIB-Z

DUNS Number: 605799469
Project Start Date: 14-SEP-2011

CFDA Code: 394
Project End Date: 31-MAR-2022

Study Section: Special Emphasis Panel (ZRG1-SBIB-Z (58)R) **Project Start Date**: 14-SEP-2011 **Project End Date**: 31-MAR-2022
Budget Start Date: 1-APR-2019 **Budget End Date**: 31-MAR-2020
Fiscal Year: 2019 **Award Notice Date**: 19-MAR-2019

Administering Institutes or Centers:

NATIONAL CANCER INSTITUTE

Project Funding Information for 2019:

Total Funding: $505,134 **Direct Costs:** $374,760 **Indirect Costs:** $130,374

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL CANCER INSTITUTE	$505,134

History:

Total project funding amount for **6** projects is **$3,160,913***

** Only NIH,CDC,and FDA funding data.*

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
5R01CA154451-06		ULTRASOUND-ENHANCED DRUG PENETRATION FOR TREATMENT OF PANCREATIC CANCER	HWANG, JOO HA	UNIVERSITY OF WASHINGTON	2019	NCI	NCI	$505,134
5R01CA154451-05		ULTRASOUND-ENHANCED DRUG PENETRATION FOR TREATMENT OF PANCREATIC CANCER	HWANG, JOO HA	UNIVERSITY OF WASHINGTON	2018	NCI	NCI	$506,176
2R01CA154451-04A1		ULTRASOUND-ENHANCED DRUG PENETRATION FOR TREATMENT OF PANCREATIC CANCER	HWANG, JOO HA	UNIVERSITY OF WASHINGTON	2017	NCI	NCI	$498,703
5R01CA154451-03		ULTRASOUND ENHANCED PENETRATION FOR TREATMENT OF PANCREATIC CANCER	HWANG, JOO HA	UNIVERSITY OF WASHINGTON	2013	NCI	NCI	$509,766
5R01CA154451-02		ULTRASOUND ENHANCED PENETRATION FOR TREATMENT OF PANCREATIC CANCER	HWANG, JOO HA	UNIVERSITY OF WASHINGTON	2012	NCI	NCI	$526,861
1R01CA154451-01A1		ULTRASOUND ENHANCED PENETRATION FOR TREATMENT OF PANCREATIC CANCER	HWANG, JOO HA	UNIVERSITY OF WASHINGTON	2011	NCI	NCI	$614,273

Subprojects:

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	FY Total Cost by IC
No Subprojects information available for 5R01CA154451-06							