Nutrition, Métabolismes et Cancer

To whom it may concern

I, undersigned Bruno Clément, head of the Institute "Nutrition, Metabolisms and Cancer", hereby certify that the works that are reported in the manuscript entitled "The dimensions of Hepatocellular Carcinoma Phenotypic Diversity" by Desert et al. were financially supported by INSERM, the French Institute of Health and Medical Research.

August 28, 2017

Bruno Clément
Research director at Inserm
Head of NuMeCan

U1241 Inserm – Inra – Université de Rennes 1
https://numecan.univ-rennes1.fr

Site Villejean-Pontchaillou
CHU Pontchaillou
2, rue Henri Le Guilloux
35033 Rennes Cedex
(+33)2.23.23.38.52

Site Saint Gilles
Domaine de la Prise
35590 Saint Gilles
(+33)2.23.48.50.52

AWARD/CONTRACT

1. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 700)	RATING	PAGE OF PAGES
		1 | 15

2. CONTRACT *(Proc. Inst. Ident.)* NO.	3. EFFECTIVE DATE	4. REQUISITION/PURCHASE REQUEST/PROJECT NO.
W81XWH1810243	15 Jul 2018	0011173523

5. ISSUED BY	CODE	6. ADMINISTERED BY *(If other than Item 5)*	CODE
USA MED RESEARCH ACQ ACTIVITY 820 CHANDLER ST FORT DETRICK MD 21702-5014	W81XWH	**See Item 5**	

7. NAME AND ADDRESS OF CONTRACTOR *(No., street, city, county, state and zip code)*	8. DELIVERY	
UNIVERSITY OF ILLINOIS OFFICE OF BUSINESS AND FINANCIAL SERVICE 809 S MARSHFIELD RM 520 CHICAGO IL 60612-4305	[ ] FOB ORIGIN [X] OTHER *(See below)*	
	9. DISCOUNT FOR PROMPT PAYMENT Net 30 Days	
	10. SUBMIT INVOICES **1** *(4 copies unless otherwise specified)* TO THE ADDRESS SHOWN IN:	ITEM
CODE 1YGW1	FACILITY CODE	

11. SHIP TO/MARK FOR	CODE	12. PAYMENT WILL BE MADE BY	CODE
W03J USA MED RESEARCH MAT CMD W03J USA MED RESEARCH MAT CMD 1077 PATCHEL STREET FORT DETRICK MD 21702-5024	W91ZSQ	DEFENSE FINANCE AND ACCOUNTING SERVICE DFAS-INDY VP GFEBS 8899 E 56TH STREET INDIANAPOLIS IN 46249-3800	HQ0490

13. AUTHORITY FOR USING OTHER THAN FULL AND OPEN COMPETITION:	14. ACCOUNTING AND APPROPRIATION DATA
[ ] 10 U.S.C. 2304(c)( ) [ ] 41 U.S.C. 253(c)( )	**See Schedule**

15A. ITEM NO.	15B. SUPPLIES/ SERVICES	15C. QUANTITY	15D. UNIT	15E. UNIT PRICE	15F. AMOUNT
	SEE SCHEDULE				

15G. TOTAL AMOUNT OF CONTRACT **$639,600.00**

16. TABLE OF CONTENTS

(X)	SEC.	DESCRIPTION	PAGE(S)
		PART I - THE SCHEDULE	
X	A	SOLICITATION/ CONTRACT FORM	1
	B	SUPPLIES OR SERVICES AND PRICES/ COSTS	
	C	DESCRIPTION/ SPECS./ WORK STATEMENT	
	D	PACKAGING AND MARKING	
	E	INSPECTION AND ACCEPTANCE	
	F	DELIVERIES OR PERFORMANCE	
	G	CONTRACT ADMINISTRATION DATA	
	H	SPECIAL CONTRACT REQUIREMENTS	
		PART II - CONTRACT CLAUSES	
	I	CONTRACT CLAUSES	
		PART III – LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACH.	
	J	LIST OF ATTACHMENTS	
		PART IV - REPRESENTATIONS AND INSTRUCTIONS	
	K	REPRESENTATIONS, CERTIFICATIONS AND OTHER STATEMENTS OF OFFERORS	
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	M	EVALUATION FACTORS FOR AWARD	

CONTRACTING OFFICER WILL COMPLETE ITEM 17 (SEALED-BID OR NEGOTIATED PROCUREMENT) OR 18 (SEALED-BID PROCUREMENT) AS APPLICABLE

17. [ ] CONTRACTOR'S NEGOTIATED AGREEMENT Contractor is required to sign this document and return copies to issuing office.) Contractor agrees to furnish and deliver all items or perform all the services set forth or otherwise identified above and on any continuation sheets for the consideration stated herein. The rights and obligations of the parties to this contract shall be subject to and governed by the following documents: (a) this award/contract, (b) the solicitation, if any, and (c) such provisions, representations, certifications, and specifications, as are attached or incorporated by reference herein. (Attachments are listed herein.)

18. [ ] SEALED-BID AWARD (Contractor is not required to sign this document.)
Your bid on Solicitation Number _____
REF: See Section 00800
including the additions or changes made by you which additions or changes are set forth in full above, is hereby accepted as to the terms listed above and on any continuation sheets. This award consummates the contract which consists of the following documents: (a) the Government's solicitation and your bid, and (b) this award/contract. No further contractual document is necessary. (Block 18 should be checked only when awarding a sealed-bid contract.)

19A. NAME AND TITLE OF SIGNER *(Type or print)*	20A. NAME OF CONTRACTING OFFICER
	JAMIE A. SHORTALL / GRANTS OFFICER TEL: (301) 619-2393 EMAIL: jamie.a.shortall.civ@mail.mil

19B. NAME OF CONTRACTOR	19C. DATE SIGNED	20B. UNITED STATES OF AMERICA	20C. DATE SIGNED
BY _____ *(Signature of person authorized to sign)*		BY _____ *(Signature of Contracting Officer)*	05-Jul-2018

Section 00010 - Solicitation Contract Form

ITEM NO	SUPPLIES/SERVICES	QUANTITY	UNIT	UNIT PRICE	AMOUNT
0001					$639,600.00
	Proposal Log# CA170172 COST Award Mechanism: FY17, PRCRP, Idea Award with Special Focus Sponsoring Agency: The Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense FOB: Destination PURCHASE REQUEST NUMBER: 0011173523 PSC CD: AN91				
				ESTIMATED COST	$639,600.00
	ACRN AA CIN: GFEBS001117352300001				$639,600.00

DELIVERY INFORMATION

CLIN	DELIVERY DATE	QUANTITY	SHIP TO ADDRESS	DODAAC / CAGE
0001	POP 15-JUL-2018 TO 14-JUL-2020	N/A	W03J USA MED RESEARCH MAT CMD W03J USA MED RESEARCH MAT CMD 1077 PATCHEL STREET FORT DETRICK MD 21702-5024 301-619-7416 FOB: Destination	W91ZSQ

Section 00800 - Special Contract Requirements

ACCOUNTING AND APPROPRIATION DATA

AA: 097201720180130000183103333335410 R.0002687.7.1 6100.9000021001
COST CODE: A7444
AMOUNT: $639,600.00

ACRN	CLIN/SLIN	CIN	AMOUNT
AA	0001	GFEBS001117352300001	$639,600.00

CLAUSES INCORPORATED BY FULL TEXT

U.S. ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY
AWARD SPECIFIC RESEARCH TERMS AND CONDITIONS
WITH INSTITUTIONS OF HIGHER EDUCATION, HOSPITALS, AND NON-PROFIT ORGANIZATIONS

DIVISION I – AWARD COVER PAGES

A. Award Information

1. **Department of Defense Awarding Office:** USAMRAA
2. **Award number/Project title:** W81XWH-18-1-0243/Role of Osteopontin in Hepatocellular Carcinoma
3. **Type of Award:** Grant
4. **Type of Award Action:** New
5. **i. Brief description of project or program:**

Background: liver carcinogenesis and its progression to hepatocellular carcinoma (HCC) is a complex process that can imply the malignant transformation of hepatocytes (Hep) to cancer stem/progenitor cells (CSCs) that generally express the CD44 receptor, while CSCs lacking CD44 show a less proliferative phenotype. The Karin Lab has shown that CD44, by decreasing the tumor suppressor gene p53, is required for carcinogenesis in the diethylnitrosamine (DEN) preclinical mouse model of HCC. We have previously demonstrated that osteopontin (OPN), a secreted protein and a major ligand for CD44, is strongly increased in liver fibrosis and HCC. Preliminary results from patients with early cirrhosis show a cluster of individuals strongly expressing OPN, which harbor less activation of the p53 target genes and show greater risk to develop HCC.

Our central hypothesis is that hepatocyte-derived OPN is a major driver of hepatocellular carcinogenesis; first, by signaling via CD44 to inhibit DNA repair, apoptosis and the cell cycle by blocking p53; and second, by driving the emergence of CSCs, increasing their maintenance and proliferation, consequently enhancing the number of HCCs.

Specific Aims & Study Design: in **Aim 1**, to dissect if OPN binding to CD44 in hepatocytes inhibits DNA repair, apoptosis and the cell cycle by blocking p53, we will focus on analyzing the signaling pathways activated upon OPN binding to CD44 and their ability to impact DNA repair, apoptosis and to cause cell cycle arrest by blocking p53. Using two *in vivo* approaches we will assess if OPN binding to CD44 activates PI3K, pAkt and pMDM2 followed by p53 ubiquitination and degradation. Alternative pathways will be explored using a phosphorproteomics approach. In **Aim 2**, to establish if hepatocyte-derived OPN stimulates the emergence of CSCs and increases their maintenance and proliferation, consequently enhancing the number of HCCs; first, we will establish if hepatocyte-derived OPN

stimulates the emergence of CSCs. We will use a well-established mouse model of HCC based on a single injection of DEN in transgenic mice overexpressing OPN in hepatocytes with or without global ablation of *Cd44* (*Opn*Hep Tg and *Cd44*-/-*Opn*Hep Tg). Mice will be injected DEN and 5 months later CSCs will be isolated from collagenase-resistant aggregates and characterized. Second, we will determine if hepatocyte-derived OPN increases CSCs maintenance and proliferation, consequently enhancing the number of HCCs. To this end, we will treat CSCs with rOPN and determine cell viability, apoptosis and differentiation. Then, CSCs will be injected in the spleen of mice expressing or not OPN in hepatocytes (WT, *Opn*ΔHep and *Opn*Hep Tg) to macroscopically assess if OPN increases the number and size of HCCs developed over time.

Our long-term objective is to dissect the molecular mechanisms whereby OPN drives hepatocellular carcinogenesis and progression, to fill the gap in our knowledge on the pathogenesis of HCC, a disease affecting the general population, which has a particularly profound impact on the health and well-being of Military Service members and US Veterans due to the prevalence of risk factors in this population.

Innovation: the role of OPN in hepatocellular carcinogenesis and progression has been poorly studied. We propose to prove the hypothesis of its carcinogenic effect via its binding to CD44 and alteration of the p53 signaling pathway. We will analyze the emergence and proliferation of CSCs. Among the numerous drugs under clinical trial for HCC, none of them targets OPN. Our project will highlight the crucial role of OPN in the pathogenesis of HCC and establish it as a promising risk factor for developing HCC and hence as a drugable target.

Military Relevance: Hepatitis C (HCV) and B (HBV) infection, alcohol abuse, obesity and nonalcoholic fatty liver disease (NAFLD) are the main risk factors for the development of HCC. The VA administration estimates that due to exposure to viruses and toxins in the battle field, Veterans have higher rates of HCV and HBV infection than the general US population. Acute and/or chronic alcohol consumption is also more common among young male military personnel compared with male civilians within a similar age range. In addition, 15% of Veterans engage in alcohol abuse within 6 months after returning from combat. Finally, over 70% of our Veterans are overweight or develop NAFLD, which is superior to the rate in the general US population. Thus, almost all the risk factors of HCC are more prevalent in US Veterans. From 2001 to 2013, the incidence of cirrhosis nearly doubled among Veterans and the HCC mortality rate nearly tripled. In 2013, the VA was treating 7,670 Veterans with HCC. Unfortunately, HCC remains difficult to treat and no recent therapy has shown convincing results. This project could identify new potential targets for future treatment that could also be used in a preventive manner in the cirrhotic population of VA patients.

ii. Funding Overview

	Federal funds	Cost Sharing	Total amount
a. Obligated or deobligated this action	$639,600	N/A	$639,600
b. Cumulative obligations to date, including this and previous actions	$639,600	N/A	$639,600
c. Planned project costs in the currently approved budget through the end of the period of performance, to include any future incremental funding obligations	$639,600	N/A	$639,600
d. Total value, which includes any unexercised options for which amounts were established in the award	$639,600	N/A	$639,600

6. **Obligation/Effective Date:** See SF-26, Block 20c.
7. **Period of performance:** 15 July 2018 – 14 July 2020
8. **Authorities:** This award is made under the authority of 10 U.S.C. 2358.
9. **Catalog of Federal Domestic Assistance Number:** 12.420-Military Medical Research and Development
10. **Project Performance Information:**

i. This award is for research and development. Construction activities under this award are not authorized. (Reference Department of the Army Pamphlet 420-11, dated 18 March 2010, for the definition of construction activities.)

ii. Statement of Work and Budget: The revised Statement of Work (SOW) dated 8 May 2018 and the revised budget dated 16 May 2018 for your application submitted in response to the Fiscal Year 2017 DoD Peer Reviewed Cancer Research Program, Idea Award with Special Focus, Program Announcement (Funding Opportunity Announcement Number W81XWH-17-PRCRP-IA, which closed 04 October 2017) are incorporated herein by reference. You may rebudget allowable costs in accordance with applicable cost principles and in accordance with the prior approval requirements as stated in this award. Additional terms and conditions applicable to this award are in Division II and Division III.

iii. The following terms and conditions are incorporated herein by reference:
   a. Division III - USAMRAA Addendum to the DoD R&D General Terms and Conditions available at http://www.usamraa.army.mil/Pages/Resources.aspx.
   b. The DoD R&D General Terms and Conditions (September 2017), available at http://www.onr.navy.mil/Contracts-Grants/submit-proposal/grants-proposal/grants-terms-conditions.aspx.

iv. These USAMRAA Award Specific Research Terms and Conditions are in addition to the terms and conditions incorporated above. Any inconsistencies in the requirements of this award will be resolved in the following order:
   a. Federal statutes
   b. Federal regulations
   c. 2 CFR part 200 with amendments, as modified and supplemented by DoD's interim implementation found in 2 CFR part 1103
   d. Division II - USAMRAA Award Specific Research Terms and Conditions
   e. Division III – USAMRAA Addendum to the DoD R&D General Terms and Conditions
   f. DoD R&D General Terms and Conditions (September 2017)

v. **Grants Administration Office**

Grants Specialist: Jaclyn Svincek
Phone: 301-619-7669
Email: Jaclyn.P.Svincek.civ@mail.mil
Assistance Agreement Branch Email: usarmy.detrick.medcom-usamraa.mbx.aa3@mail.mil

vi. **Grants Officer's Representative**

Congressionally Directed Medical Research Program Office
Phone: 301-619-7071
Email: usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil

B. Recipient Information

1. **Unique Entity Identifier:** 098987217
2. **Recipient Business Name and Address:** University of Illinois, 809 S. Marshfield RM 520, Chicago, IL 60612-4305
3. **Name and Title of Authorized Representative:** Mitra Dutta, PhD; Vice Chancellor for Research
   a. Phone: 312-996-2862
   b. Email: awards@uic.edu
4. **Principal Investigator:** Natalia Nieto
   a. Phone: 312-996-7316
   b. Email: nnieto@uic.edu
5. **Recipient's Indirect Cost Rate at the Start of the Performance Period:**
   Rate, Type, Basis, Period: 59.9%, Predetermined, MTDC, 7/1/2017-6/30/2018
   Negotiating Agency: ONR

C. Additional Information:

1. **Award Modification:** The only method by which the award may be modified is by a formal, written modification signed by the USAMRAA Grants Officer. No other communications, whether oral or in writing, are valid to change the terms and conditions of this award. Awards will not be modified to provide additional funds for such purposes as reimbursement for unrecovered indirect costs resulting from the establishment of final negotiated rates or for increases in salaries, fringe benefits, changes in exchange rates, or other costs.
2. **Expiration of Funds:** Funds obligated on this award are available for use for a limited period based on the fiscal year (FY) of the funds. That time is considered when establishing your period of performance. **This award is funded with FY17 funds in the amount of $639,600 (CLIN 0001) which will expire for use on September 30, 2023.** You must monitor the established milestones, timelines, expenditures and invoicing to make sure the project is on schedule and that you voucher promptly. If you have not submitted a final SF270 and been paid before the expiration date of these funds, any excess funds will be deobligated from the award at that time.

DIVISION II – AWARD SPECIFIC RESEARCH TERMS AND CONDITIONS

Special Requirements for Annual/Final Technical Reports

Special Requirements for Annual/Final Reports (must be submitted as an appendix to the annual/final report)

Award Charts: The Award Chart (available on https://ebrap.org/eBRAP/public/Program.htm) must be submitted at time of award and updated and submitted as an appendix to the annual and final report.

DIVISION III- USAMRAA ADDENDUM TO THE DoD GENERAL TERMS AND CONDITIONS AND USAMRAA PROGRAMMATIC REQUIREMENTS

Preamble

This award incorporates by reference the Department of Defense (DoD) Research and Development Terms and Conditions available at https://www.onr.navy.mil/Contracts-Grants/submit-proposal/grants-proposal/grants-terms-conditions . The USAMRAA Addendum to the DoD R&D General Terms and Conditions provides additional content relevant to USAMRAA awards for sections of specified articles from those general research terms and conditions. **The five asterisks indicate that there is content from the DoD R&D General Research Terms and Conditions within the identified parts and articles that remains unchanged and is not restated in this document. To understand the requirement for a given article, the DoD R&D General Research Terms and Conditions must be read in tandem with this USAMRAA Addendum.** The second portion of this addendum is comprised of the programmatic requirements portion of the general terms and conditions that apply to USAMRAA awards subject to the DoD R&D General Terms and Conditions.

USAMRAA Addendum to the DoD R&D General Terms and Conditions

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Part I: Definitions

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Section D. Definitions

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43. Intangible Property

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c. For purposes of USAMRAA awards, software is also considered intangible property.

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Part 2: Financial and Program Management (FMS Articles)

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FMS Article II. Payments

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Section C. Electronic Funds Transfer and other payment procedural instructions of information

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2. Other payment procedural instructions or information

a. Request for Payments

i. Payments. Payments will be made to you upon receipt of a "grant voucher" (used for both grants and cooperative agreements) submitted through the Wide Area Work Flow (WAWF) e-Business Suite in accordance with the Contract Line Item Number (CLIN) structure set forth in this award. The Defense Finance and Accounting Service (DFAS) will generally make payments within 30 calendar days after we receive the request for reimbursement unless we reasonably believe the request is improper.

ii. You must select "advance" or "reimbursement" on the grant voucher in WAWF.

iii. In order to conserve administrative resources for both parties, you are encouraged to voucher no more frequently than monthly. Failure to voucher at least quarterly may raise concerns about research progress and the need for continued funding.

iv. All payments will be made by Electronic Funds Transfer (EFT) to the bank account registered in the System for Award Management (SAM) (available at https://www.sam.gov). You must maintain the currency about yourself in SAM, including information necessary to facilitate payment via EFT. We cannot be held responsible for any misdirection or loss of payment which occurs as a result of your failure to maintain correct/current EFT information within your SAM registration. Failure to update SAM ensuring active account status will result in nonpayment.

b. Electronic Payment Instructions

i. The Wide Area Work Flow (WAWF) e-Business Suite is the required method to electronically process your requests for payments. Once on the WAWF e-Business Suite web site, select the Invoicing, Receipt, Acceptance, and Property Transfer (iRAPT) button to electronically submit "grant vouchers" (used for both grants and cooperative agreements). You must (i) register to use WAWF at https://wawf.eb.mil and (ii) ensure an electronic business point of contact (POC) is designated in the System for Award Management (SAM) site at https://www.sam.gov within ten (10) calendar days prior to requesting a payment for this award. The Award specific Research Terms and Conditions will include additional instructions on how to submit grant vouchers and who to contact for assistance if needed.

ii. Questions concerning specific payments should be directed to the Defense Finance and Accounting Service (DFAS), Indianapolis, at 1-888-332-7366, unless a different office is specified in Division II in your award specific terms and conditions. **You can also access payment and receipt information using the**

"myInvoice" button in WAWF at https://wawf.eb.mil. The award number or grant voucher number will be required to inquire about the status of the payment.

iii. The following codes and information are required to initiate the grant voucher and assure successful flow of WAWF documents.

TYPE OF DOCUMENT: **Grant Voucher** ***(Used for both grants and cooperative agreements)***

CAGE CODE: **Enter Your Cage Code**

ISSUE BY DODAAC: **W81XWH**

ADMIN BY DODAAC: **W81XWH**

INSPECT BY DODAAC: **W81XWH**

ACCEPT BY DODAAC: **W81XWH**

SHIP TO DODAAC: **W81XWH**

LOCAL PROCESSING OFFICE DODAAC: **Not Applicable**

PAYMENT OFFICE FISCAL STATION CODE: **Unless otherwise specified in Division II in your award specific terms and conditions enter Fiscal Station DODAAC as HQ0490 = DFAS Indianapolis**

EMAIL POINTS OF CONTACT LISTING:
INSPECTOR: **Submit to Assistance Agreement Branch Email identified in the Division I, 10.v.**
ACCEPTOR**: Submit to Assistance Agreement Branch Email identified in the Division I, 10.v.**
RECEIVING OFFICE POC: **Submit to Assistance Agreement Branch Email identified in the Division I, 10.v.**
GRANT ADMINISTRATOR: **Leave Blank**
GRANTS OFFICER: **Leave Blank**
ADDITIONAL CONTACT: **Submit to Assistance Agreement Branch Email identified in the Division I, 10.v.**

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FMS Article IV. Revision of budget and program plans.

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Section B. Revisions requiring prior approval.

1**. Non-Construction Activities**

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e**. USAMRAA Specific Prior Approval Requirements**

i. The transfer (relocation) of the PI and or research project to another entity.
ii. Reimbursing a DoD Military Treatment Facility (MTF) for costs incurred if the MTF is involved in the award. Reimbursing these costs is generally prohibited and only approved under unusual and extraordinary circumstances.

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Section C. Pre-award costs, carry forward of unobligated balances, and one-time no-cost extensions.

* * * * *

3. **No-cost Extension of the Period of Performance**

a. You may initiate one time, without prior approval, a no-cost extension to the expiration date of the award for a period of up to 12 months, as long as the no-cost extension does not involve a change in the approved objectives or scope of the project. You must notify the USAMRAA Grants Officer in writing at least 30 calendar days prior to the expiration date of the award. The notification must state the additional time needed, the reasons for the extension, and the work to be completed during the extension period. You must be current with all financial and technical reporting requirements and be in compliance with all other terms and conditions of the award. This one-time no-cost extension may not be exercised merely for the purpose of using unobligated balances. An official modification to the award document must be issued by the USAMRAA Grants Officer to extend the period of performance.

b. Reference "Expiration of Funds" in Division I Award Cover Pages to understand the impact of the availability of funds on award extensions.

c. Collaborating awards (two or more USAMRAA-issued awards completing the same Statement of Work) may have to have identical periods of performance. Each collaborating recipient's business office must contact the Grants Officer assigned to the awards regarding extensions.

d. Any subsequent no-cost extensions require prior approval from the USAMRAA Grants Officer.

* * * * *

Part 5. Financial Programmatic, and Property Reporting (REP Article)

REP Article I. Performance management, monitoring, and reporting.

Section A. Required reporting form, format, or data elements for interim and final performance reports.

1. Annual Technical Report

   a. Annual reports are required and must be prepared in accordance with the Research Performance Progress Report (RPPR). The RPPR is the uniform format for reporting performance progress on Federally-funded research projects and research-related activities. Annual reports must provide a complete summary of the research results (positive or negative) to date in direct alignment to the approved Statement of Work (SOW). The importance of the report to decisions relating to continued support of the research cannot be over-emphasized.
   b. Special Requirements for Annual Reports-Refer to Division II.

2. Final Technical Report

   a. A final report must be prepared in accordance with the RPPR. The report must summarize the entire research effort, citing data in the annual reports and appended publications.
   b. Special Requirements for Final Reports-Refer to Division II.

3. Format

Prepare the annual and final reports in accordance with the RPPR format, available at http://www.usamraa.army.mil/Pages/Resources.aspx. Although there is no page limitation for the reports, each

report must be of sufficient length to provide a thorough description of the accomplishments with respect to the approved SOW

Section B. Frequency, reporting periods, and due dates for interim performance reports.

An annual technical report must be submitted within 30 calendar days of the anniversary date of the award for the preceding 12 month period. If the award period of performance is extended by the USAMRAA Grants Officer, then an annual report must still be submitted within 30 days of the anniversary date of the award.

* * * * *

Section F. Performance Reporting Procedures

Annual and Final Technical Reports, in electronic format (PDF or Word file only), must be submitted to https://ers.amedd.army.mil.

Additional information is available on the Researcher Resources website, available at https://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting

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REP Article II. Financial Reporting.

Section A. Required reporting form, format, or date elements for interim and final financial reports.

You must submit financial reports on the Standard Form 425 (SF425) "Federal Financial Report."

Section B. Interim financial reports; frequency, reporting periods, and due dates.

The Federal Financial Reporting period end dates fall on the end of the calendar year for annual reports (12/31). You must submit annual reports no later than 90 days after the end of the calendar year.

* * * * *

Section E. Where and how to submit financial reports.

1. You must submit all interim SF425 reports electronically through the web site https://www.usamraa.army.mil/Pages/SF425.aspx. The form and instructions can be obtained on this site.

2. Do not report multiple awards on one report. Each award must be reported separately on its own SF425.

3. Do not combine multiple SF425s into one submission. Each form must be saved as a separate PDF and submitted individually.

4. You must submit Final SF425 reports electronically to usarmy.detrick.medcom-usamraa.mbx.closeout@mail.mil

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REP Article III. Reporting on Property.

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Section D. Intangible Property.

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1**. Inventions developed under this award.**

* * * * *

a. Patents and Inventions Reporting Requirements

i. iEdison and annual reporting. You must electronically file Invention Disclosures and Patent Applications using the Interagency Edison (iEdison) system through the National Institutes of Health (https://s-edison.info.nih.gov/iEdison) within the times specified for reporting.

ii. Report of Inventions and Subcontracts. A final DD Form 882 is required and must be submitted electronically within 120 days of end of the term of award. List all inventions made during the term of the award or state "none," as applicable. The award will NOT be closed until you have met all reporting requirements. Submit the final DD882 reports electronically to usarmy.detrick.medcom-usamraa.mbx.closeout@mail.mil

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Part 6: Other Administrative Requirements (OAR Articles)

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OAR Article III Remedies and termination.

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Section B. Remedies for non-compliance.

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f. If you are delinquent on technical reporting requirements for other USAMRAA-sponsored awards, no new awards will be issued to you until all delinquent reports have been submitted.

g. Failure to submit required Technical Reports or Federal Financial Reports (SF425s) may delay payments or result in nonpayment.

* * * * *

OAR Article IV. Claims, disputes, and appeals.

Section A. Definitions

* * * * *

2. Grant Appeal Authority- Lamont G. Kapec Deputy Chief of Staff, Procurement and Head of the Contracting Activity HQDA Office of the Surgeon General and U.S. Army Medical Command, 7700 Arlington Boulevard Falls Church, VA 22042-5140

* * * * *

OAR Article VI. Closeout

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Section B. Refunds of Unobligated balances.

* * * * *

a) Make check payable to the U.S. Treasury and mail to:
USAMRAA
Attn: MCMR-AAP-C
(Insert Federal Award No. W81XWH-_____)
820 Chandler Street
Fort Detrick, Maryland 21702-5014

* * * * *

Section D. Accounting for Property.

* * * * *

a) **Property Acquired with Award Funds, if applicable** [Reference PROP Article IV of the DoD R&D General Terms and Conditions (September 2017).]

i. If equipment under this award is exempt property, you must provide a cumulative listing of exempt equipment acquired with award funds. Submit this on your organization's letterhead. Submit to: Assistance Agreement Branch Email identified in the Division I, 10.v.

ii. If supplies under this award are exempt, you must submit a statement that: (i) there is, or is not, a residual inventory of unused supplies exceeding $5,000 in total aggregate value; and (ii) if there is, state whether or not the unused items will be needed on other Federally sponsored projects or programs. Submit this on your organization's letterhead. Submit to Assistance Agreement Branch Email identified in the Division I, 10.v.

* * * * *

Part 8: National Policy Requirements

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NP Article III. National policy requirements concerning live organisms.

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Section B. Other requirements concerning live organisms

1. **Research Involving Recombinant DNA Molecules** By signing the award or accepting funds under the award, you assure that all work involving the use of recombinant DNA will be in compliance with guidance provided at https://osp.od.nih.gov/biotechnology/biosafety-and-recombinant-dna-activities/.

2. **Prohibition of Use of Laboratory Animals**

Notwithstanding any other terms and conditions contained in this award or incorporated by reference herein, the recipient is expressly forbidden to use or subcontract for the use of laboratory animals in any manner whatsoever without the express written approval of the USAMRMC, Animal Care and Use Review Office (ACURO). Written authorization to begin research under applicable protocol(s) proposed for this award will be issued in the form of an approval letter from the USAMRMC ACURO to the recipient with a copy to the USAMRAA Grants Officer. Furthermore, modifications to already approved protocols require approval by ACURO prior to implementation. For each fiscal year, the recipient must maintain, and upon request from ACURO, submit animal usage information.

Noncompliance with any of these terms and conditions may result in withholding of funds and/or the termination of the award.

The Animal Care and Use Office requirements can be accessed at https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.acuro.

3. **Prohibition of Use of Human Subjects**

Research under this award involving the use of human subjects, to include research involving the secondary use of human biospecimens and/or human data, cannot begin until the USAMRMC's Office of Research Protections (ORP) provides authorization that the research may proceed. The USAMRMC ORP will issue written approval to begin research under separate notification to you. Written approval to proceed from the USAMRMC ORP is also required for any subrecipient that will use funds from this award to conduct research involving human subjects.

The USAMRMC ORP conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

The recipient is required to adhere to the following reporting requirements:

Submission of substantive modifications to the protocol, continuing review documentation, and the final report as outlined in the USAMRMC ORP approval memorandum.

Unanticipated problems involving risks to subjects or others, subject deaths related to participation in the research, clinical holds (voluntary or involuntary), and suspension or termination of this research by the IRB, the institution, the Sponsor, or regulatory agencies, must be promptly reported to the USAMRMC ORP.

Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRMC ORP HRPO.

The knowledge of any pending compliance inspection/visits by the FDA, ORP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies, and any instances of serious or continuing noncompliance with regulatory requirements that relate to this clinical investigation or research, must be reported immediately to the USAMRMC ORP.

Non-compliance with these terms and conditions may result in withholding of funds and/or the termination of the award.

DoD requirements for human subjects research, including 32 CFR Part 219, DoD Instruction 3216.02, and USAMRMC ORP Human Research Protection Office submission instructions can be accessed at https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.hrpo.

4. **Prohibition of Use of Human Cadavers**

Research, development, testing and evaluation (RDT&E), education or training activities involving human cadaveric specimens under this award shall not begin until approval is granted in accordance with the Army Policy for Use of Human Cadavers for RDT&E, Education, or Training, 20 April 2012 (https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.overview).

The USAMRMC Office of Research Protections (ORP) is the Action Office (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil) for this policy. Approval must be obtained from the USAMRMC ORP. Award recipients must coordinate with the supporting/funding Army organization to ensure that proper approvals are

obtained. ORP will issue written approvals to begin under separate notification to the recipient. Written approval to proceed from the USAMRMC ORP is also required for any subrecipient that will use funds from this award to conduct RDT&E, education or training involving human cadaveric specimens.

Recipients must promptly report problems related to the conduct of the activity involving cadavers or the procurement, inventory, use, storage, transfer, transportation, and disposition of cadavers to the USAMRMC ORP.

Recipients must maintain complete records of the activity.

The USAMRMC or designees must be permitted to observe the activity upon request and/or audit activity records to ensure compliance with the approved protocol or applicable regulatory requirements.

Non-compliance with these terms and conditions may result in withholding of funds and/or the termination of the award.

Programmatic Requirements Portion of the General Terms and Conditions

Publication, Acknowledgement, and Public Release

a. Publication. You are encouraged to publish results of the research, unless classified, in appropriate media. Submit one copy of each paper to the GOR **simultaneously** with its submission for publication. Forward copies of all publications resulting from the research to the USAMRAA Grants Officer or Grants Specialist as they become available, even though publication may in fact occur subsequent to the termination date of the award. (See Section C of the DoD R&D General Terms and Conditions for the charging of publication costs incurred after the period of performance.)

b. Acknowledgment. You agree that in the release of information relating to this award such release will include the statements below, as applicable. "Information" includes, but is not limited to, news releases, articles, manuscripts, brochures, advertisements, still and motion pictures, speeches, trade association meetings, and symposia.

   i. "The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office" and;

   ii. "This work was supported by the (enter name of sponsoring agency identified in item no.0001), through the (enter program name) under Award No. (enter award number). Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the (enter Department of Defense or U.S. Army as identified in item no.0001)."

   iii. "In conducting research using animals, the investigator(s) adheres to the laws of the United States and regulations of the Department of Agriculture."

   iv. "In the conduct of research utilizing recombinant DNA, the investigator adhered to NIH Guidelines for research involving recombinant DNA molecules."

   v. "In the conduct of research involving hazardous organisms or toxins, the investigator adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories."

c. Public release. Prior to release to the public, you must notify the USAMRAA Grants Officer and the GOR of the following: planned news releases, planned publicity, advertising material concerning project work, and planned presentations to scientific meetings. This provision is not intended to restrict dissemination of research information; the purpose is to inform the USAMRMC of planned public release of information on

USAMRMC-funded research in order to adequately respond to inquiries and to be alerted to the possibility of inadvertent release of information.

Failure to include the above statements and adhere to the above regulations, when required, may result in loss of funding and/or termination of this award.

2. **National Security**

The award is intended for unclassified, publicly releasable research. You will not be granted access to classified information. We do not expect that the results of the research project will involve classified information. If, however, in conducting the activities supported under the award, you or the PI is concerned that any of the research results involve potentially classifiable information that may warrant Government restrictions on the dissemination of the results, you must promptly notify the USAMRAA Grants Officer.

3. **Use of Non-Federal Personnel**

Some USAMRMC program offices use contractor personnel to assist the GORs with review of technical reports. All review processes are conducted confidentially. Contractor personnel are required to sign agreements to protect the confidentiality of the information. Violations by reviewers that compromise the confidentiality of the reviews may result in suspension or debarment of the individual or contractor from Federal awards.