AWARD NUMBER: W81XWH-20-1-0657

TITLE: Quantitative Proteomics-Based Prostate Cancer Prediction Models for African American and Caucasian American Military Patients

PRINCIPAL INVESTIGATOR: Cullen, Jennifer

CONTRACTING ORGANIZATION: Case Western Reserve University, Cleveland, OH

REPORT DATE: October 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

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Quantitative Proteomics-Based Prostate Cancer Prediction Models for African American and Caucasian American Military Patients

5a. CONTRACT NUMBER
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5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Jennifer Cullen
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Case Western Reserve University
10900 Euclid Avenue
Cleveland, OH 44106

Sub-award:
Pacific Northwest National Laboratory (PNNL)
902 Batelle Blvd.
Richland, WA 99354

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
NA

14. ABSTRACT

In 2023, an estimated 288,300 men will be newly diagnosed with prostate cancer and 34,700 men will die from this disease in the United States (1). The burden of disease is particularly heavy on Black/African American men, who have a 1.5-fold incidence rate and 2-fold mortality rate, as compared to White/Caucasian American men (1). However, data on determinants of prostate disease aggressiveness at time of initial cancer detection are sorely lacking. **Predictive models that simultaneously incorporate demographic, clinical, social determinants of health (SDOH), and biological data are urgently needed to identify men at earlier time points, who are fated for aggressive disease, especially for Black men, to inform treatment stratification and informed treatment decision-making.** Such models could help avoid overtreatment of clinically indolent disease, as well as spare men unnecessary repeat biopsies, which are costly in terms of dollars but also in terms of reductions in patient quality of life, and to ensure proper treatment intensity for men whose disease may be fated to metastasize. By addressing biological underpinnings in the form of protein expression of indolent versus aggressive PCa at diagnosis, as well as comparing protein expression in men who remain under suspicion for PCa but do not develop cancer, this study could have immediate relevance for informing timing, type, and intensity of treatment for men undergoing biopsy due to suspicion for PCa. Data on early markers of detection for PCa specific to African American men are very limited, potentially leading to sub-optimal care. **The overarching study objective** is to identify and validate prostate biopsy tissue-derived proteomics biomarkers of prostate disease aggressiveness, with careful examination of *any racial variation* in such markers of aggressiveness, as well as to examine the independent and joint roles of SDOHs with proteomics profiles, on prostate disease aggressiveness at time of biopsy for both Black and White men. This study builds on previously published work led by multiple co-authors. ***This proposal will focus on biological factors that may contribute to racial disparities in PCa incidence and outcomes.*** Identifying new markers of cancer aggressiveness for each racial group will allow health care providers to better tailor disease management in African American patients, and identify patients who are likely to benefit from earlier, timely treatment interventions, to improve prostate cancer outcomes and quality of life for African American patients.

15. SUBJECT TERMS

Prostate cancer, racial disparity, metastasis, African American/Black men, proteomics, Social determinants of health

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	19	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

Introduction

In 2023, an estimated 288,300 men will be newly diagnosed with prostate cancer and 34,700 men will die from this disease in the United States (*American Cancer Society, Facts and Figures, 2023*). The burden of disease is particularly heavy on Black/African American men, who have a 1.5-fold incidence rate and 2-fold mortality rate, as compared to White/Caucasian American men (1). However, data on determinants of prostate disease aggressiveness at time of initial cancer detection are sorely lacking. **Predictive models that simultaneously incorporate demographic, clinical, social determinants of health (SDOH), and biological data are urgently needed to identify men at earlier time points, who are fated for aggressive disease, especially for Black men, to inform treatment stratification and informed treatment decision-making.** Such models could help avoid overtreatment of clinically indolent disease, as well as spare men unnecessary repeat biopsies, which are costly in terms of dollars but also in terms of reductions in patient quality of life, and to ensure proper treatment intensity for men whose disease may be fated to metastasize. By addressing biological underpinnings in the form of protein expression of indolent versus aggressive PCa at diagnosis, as well as comparing protein expression in men who remain under suspicion for PCa but do not develop cancer, this study could have immediate relevance for informing timing, type, and intensity of treatment for men undergoing biopsy due to suspicion for PCa.

Reasons for such racial disparities have been extensively researched and may be a function of both biological and social determinants of cancer development and aggressiveness. Early detection, when cancer is still confined to the prostate gland, greatly improves the disease-specific survival probability. However, very little is known about the molecular determinants of prostate cancer (PCa) that contribute to metastatic potential at time of initial cancer detection. Generating race-specific information about the molecular changes that occur during the PCa disease course is key to understanding the addressing the racial disparities in PCa outcomes. Predictive models that incorporate both clinical and biological expression data are urgently needed to identify men at earlier times points in life, who are fated for aggressive disease early in the cancer care continuum, especially for AA men. ***This study specifically addresses biological factors that may contribute to racial disparities in PCa incidence and outcomes.***

There is also an unmet clinical need to identify predictors of aggressive PCa, to avoid overtreatment of clinically indolent disease but ensure proper treatment intensity for men whose disease may be fated to metastasize. Use of mass spectrometry-based **quantitative proteomics** to analyze prostate biopsy tissue is a critical and growing area in cancer research. These advanced analytic approaches will be used to generate and verify protein biomarker candidates and develop models to predict prostate cancer aggressiveness in a racially diverse cohort of men from the greater Cleveland, Ohio metro area.

The overarching study objective is to identify and validate prostate biopsy tissue-derived proteomics biomarkers of disease aggressiveness at time of prostate biopsy, with careful examination of racial variation in markers of aggressiveness, as well as the independent and joint roles of SDOHs together with proteomics profiles, on prostate disease aggressiveness at time of biopsy for both Black and White men. This study builds on previously published work led by multiple co-authors.

Keywords: Prostate cancer, racial disparity, metastasis, African American, proteomics, social determinants of health

Accomplishments for Year 2 reporting period (09/01/2022-08/31/2023):

(Listed per Aim, Major Task, and Subtask from SOW):

Under Specific Aim 1:

Major Task 1: Regulatory and Personnel

Status: Ongoing IRB monitoring and compliance, maintenance of required training and credentialing for investigative team, per institutional requirements.

Major Task 2: Data Procurement

Subtask 1: Conduct database query to determine eligible subjects with formalin-fixed, paraffin-embedded (FFPE) biopsy specimens needed for proteomics analyses.

Status: Completed for 284 eligible subjects; during the no cost extension period, Year 4, all of the final 16 subjects will be identified. Metastatic cases have been the most difficult to identify.

Subtask 2: Extract all relevant data points and perform QA/QC steps to ensure highest data quality and completeness.

Status: Completed for 284 eligible subjects; during the no cost extension period, Year 4, all data for the final 16 subjects will be identified.

Subtask 3: Lock clinical dataset and prepare/ship biospecimen data to the PNNL investigators who will be blinded to patient race and cancer status.

Status: Completed shipment for n=284 cases. Locking of clinical dataset will be completed upon identification of remaining 16 subjects to be identified during the no cost extension period, in Year 4. All biospecimen data for the n=284 subjects have been processed and shipped to PNNL, with balance across race and clinical group, with the PNNL investigative team blinded to the patient characteristics prior to experimental work.

Under Specific Aim 2:

Major Task 3: Biospecimen processing & proteomics analysis *for all patient specimens*

Subtask 1: Isobaric TMT-11 labeling based in-depth discovery analysis of a subset of FFPE biopsy samples and associated statistical analysis for selecting candidate protein biomarkers.

Status: This subtask was completed in Year 2, with the full discovery proteomics dataset delivered to CWRU team in July 2022, just before the start of Year 3 of the award.

Subtask 2a: Develop high-performance PRISM-SRM assays for the biomarker candidates as described in Aim 1 for 60 subject samples to inform the markers to be selected for the larger cohort.

Status: This subtask was initiated in Year 2, but completed in Year 3. Final decisions were made as to which new assays were needed to examine new biomarker candidates. The development of those assays was initiated at the start of Year 3 (Sept-Oct) and was completed toward the end of Year 3 (August 2023).

Subtask 2b: Expand the experimental work to 240 subject samples, based on findings from Subtask 2a based on n=60.
Status: This subtask was initiated in Year 3 and will be completed during the No Cost Extension period. As of August 31, 2023, this expansion effort was completed for n=93 subjects. Protein expression data were delivered from PNNL to CWRU (J. Cullen) in September 2023.

Subtask 3: Quantification of the biomarker candidates in a large cohort of biopsy samples using PRISM-SRM and heavy isotope-labeled internal standards.
Status: Building on the findings generated the Discovery cohort proteome dataset (n=60 men), targeted biomarker expression data were generated for an additional 93 subjects. These data were delivered to J Cullen (CWRU) in September 2023 and are the focus of interim analysis and prediction modeling. The data on the remaining n=147 (n=240-93) subjects will be generated and delivered before end of calendar year 2023.

Major Task 4: Prediction Modeling
Subtask 1: Merge proteomics data with locked clinical dataset; perform data diagnostics and transformation of variables, as needed, for modeling
Status: Ongoing data diagnostics and preliminary modeling was conducted throughout Year 3 of the award, allowing for summary and presentation of early findings at a national conference.

Subtask 2: Perform all statistical analysis (descriptive, unadjusted, multivariable, bioinformatics)
Status: Ongoing interim statistical analysis was performed in Year 3 of the award. Final models will be created in Year 4 to support all manuscripts.

Major Task 5: Publications & Presentations

Subtask 1: Prepare manuscripts for peer review
Status: Significant progress has been made in developing the first of 3 planned publications, providing a confirmatory analysis of the 5 original biomarkers published on findings from large, racially diverse surgical cohort.
A second publication is underway and will examine the novel biomarkers not previously examined. Preliminary analysis indicates there are several new markers that complement the original 5, but also offer unique explanatory power for predicting aggressive prostate disease clinical group. We will await the final targeted proteomics data before submitting this second manuscript (expected to be submitted in Spring 2024).
Finally, a third publication is planned focused on the joint roles of social determinants of health with key protein biomarkers on aggressive prostate cancer phenotype. Multiple metrics of SDOH will be considered, at varying geographic regional levels.

Subtask 2: Present findings at national scientific conferences

Status: Highlights of findings from the Discovery cohort were presented at the AACR Science of Cancer Health Disparities annual meeting in Philadelphia, PA on September 19, 2022. An abstract examining social determinants of health alongside key protein biomarkers was submitted and accepted for presentation at the 16th annual 2023 AACR Science of Cancer Health Disparities annual meeting to be held in Orlando, FL in September 2023.

In 2023-2024, we will submit two abstracts for consideration: one to the 17th annual AACR Science of Cancer Health Disparities and one to the 2023 European Society for Medical Oncology (ESMO) annual meeting in Barcelona, Spain.

No Cost Extension Period:

This Year 3 report is not the final report for this award. A request was granted for a 1-year no-cost-extension (NCE) on March 29, 2023 *(please see appendix*). This additional time will allow for the remaining expansion of the proteomics data generation (Subtask 2b) from the current n=93 patients to n=240, and for final prediction modeling, and publications to be completed and submitted for peer review.

Much of the delay in the progress for this award are attributable to the delays in Year 1 execution of inter-institutional agreements. Other less significant delays have included the loss of a key staff member at CWRU University Hospitals who was assisting with subject eligibility and biospecimen identification (hence the challenge in identifying the final 16 cases need to complete cohort size of n=300).

In the NCE period, we will accomplish identification of the final 16 cases, final targeted analysis on the remaining cohort, final predictive modeling, and submission of 2 peer review manuscripts, and submission of 2 abstracts for a national and an international scientific meeting. These efforts will be streamlined by the recent hire by Dr. Cullen of a biostatistician who is skilled in regression techniques and -omics modeling.

Monthly summary of accomplishments for Year 3 (9/1/2022 – 8/31/2023):

Sept 19, 2022: Presentation given at the 15th annual AACR Science of Cancer Health Disparities annual meeting to be presented in Philadelphia, PA

October 2022 – March 2023:

Based on data from the Discovery cohort analysis, selection of new markers was discussed and final list was solidified. New assay development was initiated for the PNNL mass spec platform.

March 2023:

Request granted for a 1-year no cost extension

April 2023 – July 2023:

Final creation and implementation of novel assays for generation of targeted proteomics data for the first 93 of 240 Verification Phase cohort cases.

Submission of Abstract based on early prediction model of discovery cohort for national scientific conference.

Manuscript preparation underway for first of 3 planned papers.

August 2023-September 2023:

Acceptance of abstract for poster presentation at AACR Science of Cancer Health Disparities 16th annual meeting in Orlando, FL September 30, 2023.

Delivery of proteomics data for the first 93 of 240 Verification Phase cohort cases. Interim analysis and data cleaning/quality control. Descriptive analysis and univariate associations completed.

Impact:

One in six American men will be diagnosed with prostate cancer (PCa) during his lifetime. The burden of this disease disproportionately impacts African American (AA) men who demonstrate 1.5-times the incidence rate and 2 times the mortality rate compared to Caucasian American men. If PCa is detected early, patient outcomes are greatly improved. But there is an unmet clinical need to identify early predictors of PCa aggressiveness. Such markers could help avoid overtreatment of clinically indolent disease, which is costly in terms of dollars but also in terms of reductions in patient quality of life, and to ensure proper treatment intensity for men whose disease may be fated to metastasize.

A unique aspect of the study cohort that will be leveraged in this proposal is its large subset of men who were under *suspicion for prostate cancer* but who have undergone multiple, negative transrectal ultrasound (TRUS)-guided biopsies and persistently show no evidence of cancer. Such biopsy negative patients serve as an ideal comparison group to men detected with prostate cancer since both groups have been subjected to the same rigor of cancer ascertainment.

Short term study impact:
By addressing biological underpinnings in the form of protein expression of indolent versus aggressive PCa at diagnosis, as well as comparing protein expression in men who remain under suspicion for PCa but do not develop cancer, this study could have immediate relevance for informing timing, type, and intensity of treatment for men undergoing biopsy due to suspicion for PCa. While findings will need to be confirmed in other health care settings, a key advantage to studying the proposed aims in this study cohort will be the potential impact on improving treatment decision making in African American men.

Long-term study impact:
The findings of this project will also provide comprehensive race-specific data for the prostate disease course—for those under suspicion for PCa, to those with indolent versus aggressive disease. This patient cohort is racially diverse which makes this study setting optimal for examining cancer health disparities. The markers examined could elucidate who can be spared repeat biopsy in the future, as well as how to optimize the cancer care of African American men.

Changes/Problems: *None to report*

Products:

1. **Poster Presentation** at the American Association of Cancer Research (AACR) Science of Cancer Health Disparities 15th annual meeting in Philadelphia, PA, September 19, 2022.

2. **Abstract** (accepted) for the American Association of Cancer Research (AACR) Science of Cancer Health Disparities 16th annual meeting in Orlando, FL September 30, 2023.

3. **Generation of raw dataset** for the Aim 1 Discovery Phase cohort (n=60) containing over 10,000 proteins identified on each of the 60 men. This represents generation of the entire observable proteome. This phase of the study has informed the selection of biomarkers candidates for the Verification Phase.

Participants & Other Collaborating Organizations:

Special Reporting Requirements: *NA*

Appendices:

1. Poster presented at American Association of Cancer Research (AACR), Science of Cancer Health Disparities meeting, Philadelphia, PA, September 19, 2022.
2. No Cost Extension approval

Biological and neighborhood-level social drivers of aggressive prostate disease among Black and White men

Abstract

Introduction and study purpose: Prostate cancer (PCa) is the leading type of newly diagnosed cancer and second leading cause of cancer death in American men. Significant racial differences in PCa incidence and mortality have been long-reported in the U.S., with Black men demonstrating a disproportionately higher burden of disease compared to White men. However, some studies conducted in equal access health care settings have revealed equivalent PCa outcomes for White and Black men, including disease-specific and overall survival. Identification of early predictors of prostate disease aggressiveness is essential to avoid over-treatment of clinically favorably disease that is unlikely to progress. This study examines the independent and joint roles of biological and social determinants of health (SDOHs) in predicting prostate disease aggressiveness in a racially diverse cohort of men undergoing biopsy for suspicion of PCa.

Methodology: A retrospective cohort study was conducted at the University Hospitals (UH) Seidman Cancer Center in Cleveland, Ohio for the period January 1, 2005-December 2022. A retrospective chart review was conducted to identify eligible men, including White and Black men undergoing transrectal ultrasound-guided biopsy whose biopsy results included the following 3 groups: (i) negative biopsy with a history of 1+ negative biopsy (-ies) and no history of prostate cancer; (ii) biopsy-detected PCa of Gleason sum 6; and (iii) biopsy-detected PCa with metastasis (-es) at initial cancer detection. Detailed clinical and biological specimen data were abstracted during retrospective chart review, and quantitative proteomics analysis of FFPE biopsy tissues using mass spectrometry has been conducted at the Pacific Northwest National Laboratory (PNNL). Residential addresses were used to link each man to his census-block group Area Deprivation Index (ADI) score, as a metric of SDoHs. Students t-tests, ANOVAs and Pearson correlation analysis have been performed on the first 60 eligible subjects.

Results: This study has generated the entire proteome on the first 60 eligible subjects ("Discovery cohort") and SDoH metrics have been linked to the first 284 of 300 eligible subjects. Among the first 60 subjects, there was strong separation in proteome profiles for metastatic PCa cases but little separation of Gleason 6 and biopsy negative subjects was observed. Interesting, among the proteins that showed significant correlation with clinical group (*i.e.,* metastatic, biopsy Gleason 6, biopsy negative), few proteins were also significant correlated with subject race. However, several of those proteins were strongly associated with SDoHs.

Conclusions: Identifying new markers of cancer aggressiveness within and across race has the potential to tailor disease management and identify patients who are likely to benefit from earlier, timely treatment interventions, which will ultimately improve prostate cancer outcomes and quality of life. Upon completion of targeted proteomic analyses, we will perform multi-level modeling to predict prostate disease aggressiveness as a function of protein biomarker candidates in combination with census block group-level SDOHs. Additional SDOH metrics will also be examined, including the Social Vulnerability Index, the Ohio Opportunity Index, and the EnvironAtlas Toxic Release Inventory. We expect that these findings will improve our understanding of which men can be safely spared repeat biopsies while under suspicion for PCa, as well as optimize cancer care.

AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE	PAGE OF PAGES
S	1 | 7

2. AMENDMENT/MODIFICATION NO.	3. EFFECTIVE DATE	4. REQUISITION/PURCHASE REQ. NO.	5. PROJECT NO.(If applicable)
P00001	29-Mar-2023	0011430372	

6. ISSUED BY	CODE	7. ADMINISTERED BY (If other than item 6)	CODE
USA MED RESEARCH ACQ ACTIVITY 820 CHANDLER ST FORT DETRICK MD 21702-5014	W81XWH	ARMY MED RES ACQ ACTIVITY 808 SCHREIDER ST FORT DETRICK MD 21702	HT9425

8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code)		
CASE WESTERN RESERVE UNIVERSITY 10900 EUCLID AVE CLEVELAND OH 44106-1712		9A. AMENDMENT OF SOLICITATION NO.
		9B. DATED (SEE ITEM 11)
	X	10A. MOD. OF CONTRACT/ORDER NO. W81XWH2010657
	X	10B. DATED (SEE ITEM 13) 01-Sep-2020
CODE 4B566	FACILITY CODE	

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

☐ The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offer ☐ is extended, ☐ is not extended.

Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods: (a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA (If required)

13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS. IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

☐ A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.

☐ B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).

☐ C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:

X D. OTHER (Specify type of modification and authority)
IAW Award T/Cs and Mutual Agreement

E. IMPORTANT: Contractor ☒ is not, ☐ is required to sign this document and return _____ copies to the issuing office.

14. DESCRIPTION OF AMENDMENT/MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.)
Modification Control Number: esmith1232447

PROJECT TITLE: Quantitative Proteomics-Based Prostate Cancer Prediction Models for African American and Caucasian American Military Patients
PRINCIPAL INVESTIGATOR: Dr. Jennifer Cullen
PERIOD OF PERFORMANCE: 9-1-2020 to 8-31.2023
AWARDED AND OBLIGATED AMOUNTS:
The purpose of this modification is to extend the period of performance by 12 months at no additional cost to the Government, per the recipient's request dated 17 March 2023. An annual technical progress report is due on 1 October 2023. The final technical report is due within 120 days after POP expiration. Submission of SF425 financial reports shall continue during the extension period. See SUMMARY OF CHANGES FOR P00001 for important administrative changes to this award.

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER (Type or print)		16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print) JOSHUA MCKEAN / GRANTS OFFICER TEL: 301-619-4046 EMAIL: joshua.d.mckean3.civ@health.mil	
15B. CONTRACTOR/OFFEROR _____ (Signature of person authorized to sign)	15C. DATE SIGNED	16B. UNITED STATES OF AMERICA BY _____ (Signature of Contracting Officer)	16C. DATE SIGNED 29-Mar-2023

SECTION SF 30 BLOCK 14 CONTINUATION PAGE

SUMMARY OF CHANGES

SECTION 00010 - SOLICITATION CONTRACT FORM

The 'issued by' organization has changed from
USA MED RESEARCH ACQ ACTIVITY
820 CHANDLER ST
FORT DETRICK MD 21702-5014
to
ARMY MED RES ACQ ACTIVITY
808 SCHREIDER ST
FORT DETRICK MD 21702

The 'administered by' organization has changed from
USA MED RESEARCH ACQ ACTIVITY
820 CHANDLER ST
FORT DETRICK MD 21702-5014
to
ARMY MED RES ACQ ACTIVITY
808 SCHREIDER ST
FORT DETRICK MD 21702

CLIN 0001

The PSC code has changed from AN13 to AN11.
The NAICS code has changed from 541712 to 541715.

DELIVERIES AND PERFORMANCE

The following Delivery Schedule item for CLIN 0001 has been changed from:

DELIVERY DATE	QUANTITY	SHIP TO ADDRESS	DODAAC / CAGE
POP 01-SEP-2020 TO 31-AUG-2023	N/A	FORT DETRICK - CDMRP FORT DETRICK - CDMRP 1120 FORT DETRICK FREDERICK MD 21702 FOB: Destination	W91ZSQ

To:

DELIVERY DATE	QUANTITY	SHIP TO ADDRESS	DODAAC / CAGE
POP 01-SEP-2020 TO 31-AUG-2024	N/A	CONG DIR MED RES PRGM / CDMRP - MM 1077 PATCHEL STREET FORT DETRICK MD 21702 FOB: Destination	HT0989

The following have been added by full text:

SUMMARY OF CHANGES P00001

The purpose of this modification is:

1.

Per section 711 of the National Defense Authorization Act (NDAA) 2019, the US Army Medical Research Acquisition Activity (USAMRAA), US Army Medical Research and Development Command (USAMRDC) transferred to the Defense Health Agency (DHA) from the U.S. Army effective 01 October 2022. This modification reflects changes consistent with the transfer to DHA.

2.

Division II has been updated to supersede Division III, Part 2, Section C, 2.b. Electronic Payment Instructions

SECTION 00800 - SPECIAL CONTRACT REQUIREMENTS

The following have been modified:

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 20 1 0657 / Quantitative Proteomics-Based Prostate Cancer Prediction Models for African American and Caucasian American Military Patients
3. **Type of Award:** Grant
4. **Type of Award Action:** Modification
5. **i. Brief description of project or program:**

   Background: In 2019, an estimated 174,650 men will be newly diagnosed with prostate cancer and 31,620 men will die from this disease in the United States. The burden of disease is particularly heavy among African Americans (AA), who have a 1.5-fold incidence and 2.5-fold mortality rates, as compared to Caucasian Americans. However, data on determinants of aggressiveness of PCa at time of initial cancer detection are sorely lacking. The importance of generating race-specific information about the PCa disease course is high. Predictive models that incorporate both clinical and biological expression data are urgently needed to identify men at earlier times points, who are fated for aggressive disease, especially for African American men.

   Study Objectives: The overarching study objective is to elucidate biopsy tissue-derived proteomics biomarkers of prostate cancer development and lethality at time of initial prostate cancer detection, with an emphasis on examining racial variation in such markers of aggressiveness. This proposal specifically addresses biological factors that may contribute to racial disparities in PCa incidence and outcomes.

   Primary Study Aims:

   Aim 1: To conduct a global deep discovery analysis among African American and Caucasian military patients to develop a model based on biopsy-tissue derived proteomic markers that can distinguish between three groups of men:

a. men under suspicion for prostate cancer but who have no evidence of disease based on 2 or more negative TRUS-guided biopsy procedures
b. men who are detected with metastatic (i.e., N+/M+) prostate cancer at initial diagnosis
c. men who are detected with indolent (cT1-2a, Gleason sum <6) prostate cancer at diagnosis
Aim 2: Quantitative proteomic biomarkers of prostate cancer development and aggressiveness from both our preliminary data that was based on RP as the tissue source and biomarkers from Aim 1 above, using earliest biopsy tissue available will be verified in an expanded retrospective cohort using sensitive, precise and multiplexed targeted proteomic assays, with an emphasis on examining the role of patient self-reported race/ethnicity, to help distinguish these 3 cohort subsets (a-c above). Novel markers discovered in Aim 1 will be of interest, as will the validation of markers already identified in the preliminary study conducted (see below).
Study Design: The study population will be composed of male military patients self-reporting as African American (AA) and Caucasian American (CA) who underwent one or more transrectal ultrasound (TRUS)-guided biopsies for suspicion of PCa at the Walter Reed National Military Medical Center, a contributing center to the Center for Prostate Disease Research (CPDR) Multi-Center National Database which contains detailed clinical data collected over 25 years on more than 29,500 men, of who roughly one-third (~10,000) remain "cancer free", based on multiple TRUS biopsies, and two thirds are biopsy-confirmed for PCa (~20,000). Patients enrolled into this database at WRNMMC are also asked to consent to donate biological specimens, including biopsy tissue, which will be used in this study for quantitative proteomics analysis using mass spectrometry.
Preliminary Data: The PNNL and CPDR teams leading this grant proposal have successfully worked together since 2013, as collaborative members of the NCI Early Detection Research Network (Cullen, Rodland, Liu). Together, they have successfully used FFPE prostatectomy specimens from CPDR's clinical and biospecimen repositories for quantitative targeted proteomics analysis at PNNL, to evaluate markers of post-treatment disease progression, including biochemical progression and distant metastasis. This current study expands on this prior work by examining proteomics markers of aggressive prostate cancer at time of initial Pca detection, prior to cancer treatment, using FFPE biopsy tissue from earliest biopsy, and leveraging a unique cohort of military patients.
Impact: The findings of this project will provide the first and most comprehensive race-specific data for the entire prostate cancer disease course. All patients examined in this study will include male military health care beneficiaries seen at WRNMMC. This patient cohort is racially diverse which makes this study setting optimal for examining cancer health disparities. Moreover, the investigators are positioned to examine cancer aggressiveness which may differ in a cohort of men who have served in the armed forces.

ii. Funding Overview

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

6. **Obligation/Effective Date:** See SF-26, Block 20c.
7. **Period of performance:** 01 September 2020 – 31 August 2024
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.)
11. Statement of Work and Budget: The revised Statement of Work (SOW) dated 18 June 2020 and the revised budget dated 25 March 2020 for your application submitted in response to the Fiscal Year 2019 DoD Prostate Cancer Research Program Announcement (Funding Opportunity Announcement Number W81XWH-19-PCRP-HDRA, which closed 18 July 2019) 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.
12. 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.health.mil/Pages/Resources.aspx.
    b. The DoD R&D General Terms and Conditions (July 2018), available at: https://www.nre.navy.mil/work-with-us/manage-your-award/manage-grant-award/grants-terms-conditions
13. 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 (July 2018)
14. **Grants Administration Office**
    Grants Specialist: Erin Smith
    Phone:
    Email: erin.c.smith31.civ@health.mil
    Assistance Agreement Branch Email: usarmy.detrick.medcom-usamraa.mbx.aa4@health.mil
15. **Grants Officer's Representative**
    Congressionally Directed Medical Research Program Office
    Phone:
    Email: lymor.r.barnhard.civ@health.mil

B. Recipient Information

1. **Unique Entity Identifier:** HJMKEF7EJW69
2. **Recipient Business Name and Address:** Case Western Reserve University, 10900 Euclid Ave Cleveland, OH, 44106-1712
3. **Name and Title of Authorized Representative:** Ilene Gertman
    a. Phone:
    b. Email: Isg14@case.edu
4. **Principal Investigator** (PI) **and Organization:** Jennifer Cullen
    a. Phone:
    b. Email: jxc1650@case.edu
5. **Recipient's Indirect Cost Rate at the Start of the Performance Period:**

Rate, Type, Basis, Period: (61%, Predetermined, MTDC, 07/01/2020-06/30/2021)
Negotiating Agency: DHHS

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 FY2019 funds (CLIN 0001) which will expire for use on September 30, 2025**. 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 grant voucher 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

Award-Specific Conditions

Electronic Payment Instructions

a. 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.
b. Questions concerning specific payments should be directed to the Defense Finance and Accounting Service (DFAS) Indianapolis at 1-888-332-7366. 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.
c. 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: HT9425
ADMIN BY DODAAC: HT9425
INSPECT BY DODAAC:HT9425
GRANT APPROVER DODAAC: HT0983
SHIP TO DODAAC: HT9425
LOCAL PROCESSING OFFICE DODDAC: Not Applicable
PAYMENT OFFICE FISCAL STATION CODE: HQ0490 = DFAS Indianapolis
EMAIL POINTS OF CONTACT LISTING:
INSPECTOR: usarmy.detrick.medcom-usamraa.mbx.aa4@health.mil
ACCEPTOR: usarmy.detrick.medcom-usamraa.mbx.aa4@health.mil
RECEIVING OFFICE POC: usarmy.detrick.medcom-usamraa.mbx.aa4@health.mil
GRANT ADMINISTRATOR: Leave Blank
GRANTS OFFICER: Leave Blank
ADDITIONAL CONTACT: usarmy.detrick.medcom-usamraa.mbx.aa4@health.mil

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 Expiration Transition Plan: The Award Expiration Transition Plan (available on https://ebrap.org/eBRAP/public/Program.htm) must be submitted as an appendix to the final report.

Subaward Costs

This award contains funds for one or more subawards. The recipient, as the direct and primary recipient of USAMRAA grant funds, is accountable to USAMRAA for the project performance, the appropriate expenditures of grant funds by all parties, and all other obligations of the recipient, as specified in Part 7, Subawards, of the DoD R&D General Terms and Conditions. In general, the requirements that apply to the recipient, also apply to the subrecipient.

(End of Summary of Changes)