AWARD NUMBER: W81XWH-16-1-0584

TITLE : A Single Missense Mutation in 77% of Prostate Cancer Bone Metastases: Novel Opportunity for Genetic Biomarker and Novel Therapeutic Mitochondrial Target

PRINCIPAL INVESTIGATOR: John A. Petros, MD

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A Single Missense Mutation in 77% of Prostate Cancer Bone Metastases: Novel Opportunity for Genetic Biomarker and Novel Therapeutic Mitochondrial Target

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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Emory University, Atlanta
University of Washington,
Seattle
Cold Spring Harbor, NY

8. PERFORMING ORGANIZATION REPORT NUMBER

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Approved for Public Release;
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13. SUPPLEMENTARY NOTES

14. ABSTRACT
The purpose of this project is to determine the frequency of a mitochondrial DNA mutation at nucleotide position 10398 in the ND3 gene in prostate cancer tissues and metastases, especially bone metastases and to perform experiments in mice to determine whether the observed mutation enables or enhances bone metastases and the lethal phenotype of prostate cancer. The major findings to date are that over 50% of an expanded cohort of patients do indeed harbor the mutation in a bone-metastasis-specific fashion. Mechanistic studies in cell lines and mice are in progress with no conclusions at this early point in the project. The results to date are significant and may have broad applicability to the influence of the mitochondrial genome to cancer phenotype, especially metastasis. The model systems under development may allow mechanism to be determined.

15. SUBJECT TERMS
Prostatic Neoplasms, mitochondrial DNA, Metastasis, Mouse models of cancer

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

We have previously published that a single missense mutation in the mitochondrially encoded ND3 gene is found almost exclusively in prostate cancer bone metastases and not in normal tissue or soft tissue metastases. The purpose of this research is to increase the number of human specimens analyzed and to perform laboratory experiments (both in vitro and in vivo) to determine if the mutation is functional in cancer biology and enabling bone metastases.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Prostatic neoplasm, mitochondrial DNA, Metastasis, bone, mutation, cancer genomics.

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

(NOTE: Site 1 is Emory University, Site 2 is University of Washington and Site 3 is Cold Spring Harbor)

A. Specific Aim 1 Patient Samples	Months	Site
Major Task 1: IRB/regulatory		
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Subtask 2: IRB at sites 1 and 2	5-6	1,2
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Major Task 4: Data analysis	12-18	1
Subtask 1: Expression profiling		
Subtask 2: Pathway analysis		
Subtask 3: MtDNA sequence analysis		
Milestone Achieved: Publication of analysis of human tissues	24	1,2

[**Specific Aim 1 completion at 12 months**: Major Task 1 = 75% complete (second HRPO authorization pending – IRB approval completed); Major task 2 = 100% completed; Major task 3 = 0% completed (have concentrated on DNA assay first thus RNA assays moved to second year); Major task 4 = 0 % completed (not scheduled for first year)' Milestone: not due for another year.]

B. Specific Aim 2 Human tumor nude mouse xenografts		
Major Task 1: IACUC/regulatory		
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Milestone Achieved: Publication of analysis of human xenograft studies 36

[**Specific Aim 2 completion at 12 months**: Major Task 1= 50% complete (IACUC approved but ACURO pending – animal studies not started yet); Major task 2 = 25% complete (mutant and wild type cybrids successfully made however fusion DNA not stable with passage in culture – we have therefore concentrated on allotropic expression approach); Major Task 3 = 0% (not attempted due to loss of cybrids as explained); Major Task 4 = 25% completed (Flag tagged vectors of ND3 without or with the mutation at mtDNA 10398 have been developed, sequence verified. We have had some success with transient expression in LNCaP cells and are currently testing a variety of cell lines for expression levels as well as developing stable cell lines.); Major Task 5: 0% completed (awaiting completion of allotopic expression cell lines – not proposed until second and third year of award); Milestone = 0% (not proposed until end of award)]

C. Specific Aim 3 Genetically modified mouse analysis of mutant ND3

Major Task 1: IACUC/regulatory		
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Subtask 1: Expression profiling		
Subtask 2: MtDNA Sequence analysis		
Milestone Achieved: Publication of analysis of GMM model studies	36	

[Specific Aim 3 completion at 12 months: Major task 1 = 100% complete; Major Task 2 = 40% complete (expression vector received from Petros lab being tested in mouse cells in Trotman lab); Major Task 3 = 20% complete (designing a lentiviral expression vector with CRE and testing positive controls); Major Task 4 = 0% (not scheduled until year 3); Milestone = 0 %, (not scheduled until end of award).

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Site 1: Emory University

Frozen tissue samples from thirty two patients, including uninvolved tissue, tissue from a soft metastatic site and from a bone metastatic site were identified by University of Washington and shipped to Emory University for DNA extraction. In addition, prostate tissue from 4 of the 32 patients was also identified and transferred to Emory for analysis

After DNA extraction, digital drop PCR was performed on the DNA to determine the level of somatic mutation at mtDNA position 10398 present in the various tissue identified above. RNA purification has not been performed to date.

The principal experimental finding for this period is that we have completed the analysis of 26 patients' specimens with a targeted TaqMan assay for the identification of the 10398 nucleotide position in the mitochondrial genome. This is the base that was found to be mutated in a bone-specific fashion in 13 prostate cancer patients with bone metastasis (*Bone 78 (2015) 81-86*). We have defined the incidence of this single base alteration in an expanded series of patients and determined whether the prostate primary also harbored this mutation or if it occurred de-novo in the bone using an ultra-sensitive assay. We developed a digital drop PCR (ddPCR) fluorescent assay using the RainDance platform designed to quantitatively interrogate the mitochondrial DNA (mtDNA) nucleotide position 10398 missense mutation.

Clinical specimens from a rapid autopsy program included 39 patients (includes patients previously analyzed) with multiple tissues available including the prostate primary, soft tissue metastases, bone metastases and normal tissue controls. The number of DNA molecules with the wild type and mutant base were counted and mutation levels compared between normal tissue, primary tumor and metastatic sites.

Of 39 patients with bone metastasis that were evaluated, 20 (51%) had significantly increased levels of the 10398 missense mutation in the mitochondrially encoded ND3 gene compared to normal uninvolved tissue. The increase ranged from 2.5-59 fold in the bone. Because of the ultra-sensitive nature of the ddPCR assay used, we also identified the same base alteration in 2 lymph node metastases and one adrenal metastasis. None of the 5 primary prostate tissues examined had definitive evidence of increased mutational burden compared to normal tissue.

In this expanded cohort of 39 patients with prostate cancer bone metastases, the majority (51%) had a substantially increased level of missense mutation at the 10398 nucleotide position of the mitochondrial genome. This mutational "hot-spot" is unprecedented in frequency in prostate cancer and implies a strong selective pressure for bone metastatic cells that had acquired this mutation in the ND3 gene of respiratory complex 1. A smaller number of soft-tissue metastases also demonstrated enrichment of this mutation. The primary cancer in the prostate did not demonstrate the mutation indicating that the mutation is acquired during the process of metastasis after the pre-metastatic cell has left the prostate. This finding that the exact same missense mutation is present in over 50% of patients prostate cancer bone metastases far exceeds any somatic mutation previously reported in prostate cancer suggesting functional importance.

In vitro analysis of cybrids has not been accomplished. After development of the mutant and wild type cells, propagation of the cybrid cells resulted in the loss of the fused mtDNA and/or the a loss of viability of the cells making in vitro analysis not possible. We decided to concentrate our efforts on allotropic expression.

Flag tagged vectors of ND3 without or with the mutation at mtDNA 10398 have been developed, sequence verified. We have had some success with transient expression in LNCaP cells and are currently testing a variety of cell lines for expression levels as well as developing stable cell lines.

Site 2: University of Washington:

The work at the University of Washington was to initiate a formal and robust review of the tissue database in the GU Cancer Research laboratory to identify tissue blocks of prostate cancer metastases and, in a small number of cases, the paired primary prostate cancer. Drs. True and Morrissey were responsible for the histological assessment of the materials - characterizing tumor cell purity and other histological features to address any issues of tissue processing that might impair quality of the tissue and, thus, the findings. Dr. Morrissey was to apply for access to the tissues and de-identified information through an IRB gatekeeping form. An accurate assessment of the tissues from 32 patients was to be provided and up to 3 specimens/ patient were to be processed to provide sufficient material for DNA and RNA extraction. A material transfer agreement was to be completed and the specimens were to be shipped with paired de-identified clinical data for analysis.

Tissue specimens were identified by Ms. Nghiem. The histopathological features were characterized by Dr. True. Approvals were obtained and a pilot assessment of paraffin embedded and frozen tissues from five patients (with 3 specimens/ patient) were sent to the lead site at Emory. Subsequently, frozen tissue from a further 27 patients were provided with 3 specimens/ patient (Including 5 matching cases of primary prostate cancer) were sent to Dr. Petros at

Emory University. De-identified clinical data were abstracted for analysis. These data will not be sent to Emory University until all of the specimens have been analyzed.

Site 3: Cold Spring Harbor

Dr. Trotman's team has begun the in vitro testing of ND3 expressing plasmids that they received from Dr. Arnold. Specifically, they investigate the pCDNA3.1 based expression plasmid that contains a mitochondrial targeting sequence, a FLAG-tag, ND3-wt or ND3 mutant. They have been tested in prostate cancer cell lines and in mouse cells that are Pten/ p53 mutant. Currently they are validating localization to mitochondria using the FLAG tag in combination with mitochondrial immunostaining using the TOM20 protein.

At the same time Dr. Trotman's team has designed a lentiviral validation vector for efficient expression of any transgene in the current version of RapidCaP. This vector expresses CRE recombinase to generate Pten/ p53 deficient and TomatoFP positive cells after infection of prostate epithelial cells. In addition it contains a transgene insertion site where the ND3 inserts will be placed. Currently they are testing a positive control in vitro by infection and in vivo by injection. They use expression of the Myc transgene, the published driver of proliferation in their in vitro systems, as well as in the RapidCaP system.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During the next reporting period we expect to increase the number of human clinical samples transferred from University of Washington to Emory for DNA and RNA analysis. This is expected to actually go beyond the number of samples proposed since the results have been so interesting. In addition, the RNASeq analysis of clinical samples is expected to begin. We expect to make progress in the allotropic expression of ND3 in cell lines and animals. We also expect to begin lentiviral transfections of animals in the RAPIDCaP model system.

4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

In this expanded cohort of 39 patients with prostate cancer bone metastases, the majority (51%) had a substantially increased level of missense mutation at the 10398 nucleotide position of the mitochondrial genome. This mutational "hot-spot" is unprecedented in frequency in prostate cancer and implies a strong selective pressure for bone metastatic cells that had acquired this mutation in the ND3 gene of respiratory complex 1. A smaller number of soft-tissue metastases also demonstrated enrichment of this mutation. The primary cancer in the prostate did not demonstrate the mutation indicating that the mutation is acquired during the process of metastasis after the pre-metastatic cell has left the prostate. This finding that the exact same missense mutation is present in over 50% of patients' prostate cancer bone metastases far exceeds any somatic mutation previously reported in prostate cancer suggesting functional importance.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Other cancer types may also investigate whether mitochondrial DNA mutations enhance the metastatic phenotype.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*

- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. CHANGES/PROBLEMS: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Nothing to report.

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

No significant changes.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

While for Aim 2 the cybrid approach is not working well, progress continues with the alternate method of ND3 expression (allotropic expression). This is as according to plan.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

No significant impact on expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

None.

Significant changes in use or care of vertebrate animals

No significant changes. Some delay in Aim 2 in vivo animal experiments as described.

Significant changes in use of biohazards and/or select agents

None.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

Nothing to report.

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  none

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  None

  Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

  none

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  None

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

None

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

None

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

none

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Emory University (Site 1):

Name: John A. Petros, MD
Project Role: Overall PI
Person Month worked: 3
Contribution to Project: Design experiments, regulatory submissions, coordinate all sites
Funding Support: Institutional “Synergy” award to identify genetic predisposition to RCC

Name: Rebecca S. Arnold, PhD
Project Role: CO-PI
Person Month worked: 4
Contribution to Project: Perform Aim 2 experiments and supervise research specialist; data analysis
Funding Support: No Change

Name: Carrie Q. Sun. MD
Project Role: Research Specialist
Person Month worked: 6
Contribution to Project: Perform Aim 2 experiments, specimen banking and transfer
Funding Support: No Change

University of Washington (Site 2):

1. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**
- Dr. Lawrence True

Name:	*Lawrence True*
Project Role:	*Professor*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. True assessed all specimens with Ms. Nghiem before processing and shipping*
Funding Support:	*NA*

- Dr. Colm Morrissey

Name:	*Colm Morrissey*
Project Role:	*Research Associate Professor*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Morrissey obtained all approvals, and supervised Ms. Nghiem throughout the project*
Funding Support:	*NA*

- Belinda Nghiem

Name:	*Belinda Nghiem*
Project Role:	*Research Scientist*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*1*
Contribution to Project:	*Ms. Nghiem identified processed and shipped the specimens required to Dr. Petros at Emory*
Funding Support:	*NA*

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

- Other support Morrissey

Title: Clinical Targeting of Prostate Cancer Dormancy (Aguirre-Ghiso)
Time Commitment: 0.6 calendar
Supporting Agency: V Foundation
Sponsor Contact: Icahn School of Medicine Mount Sinai
Performance Period: 11/1/2016 – 10/31/2017
Level of Funding: $25,029
Goals/Aims: Our hypothesis is that microenvironmental signals can instruct proliferative disseminated tumor cells (DTCs) to enter dormancy by activating quiescence, pluripotency and survival programs. We also propose to test specific biomarkers that may predict dormant vs. active states of DTCs.
Role: Co-Investigator
Overlap with proposed research: None

Title: Targeting AR-NULL CRPC, W81XWH-17-1-0414 (Morrissey)
Time Commitment: 3.0 calendar
Supporting Agency: US Department of Defense
Sponsor Contact: Janet Kuhns, janet.p.kuhns.civ@mail.mil, 301-619-2827.
Performance Period: 07/01/2017 – 06/30/2020
Level of Funding: $805,613
Goals/Aims: Targeting the Mechanisms Driving Double-Negative Basal-Like Prostate Cancer. The goal of this application is to identify targets for the treatment of androgen receptor null castration-resistant prostate cancer in *in vitro* and pre-clinical models of disease.
Role: PI
Overlap with proposed research: None

Cold Spring Harbor (Site #3):

Name: Lloyd Trotman, PhD
Project Role: PI
Nearest person month worked: 0
Contribution to Project: trains staff, coordinates study

Name: Irene Casanova Salas, PhD
Project Role: Postdoc
Nearest person month worked: 1
Contribution to Project: carries out in vitro work

Name: Grinu Mathew, PhD
Project Role: Postdoc
Nearest person month worked: 0
Contribution to Project: carries out in vitro work

Name: Kaitlin Watrud
Project Role: Technician
Nearest person month worked: 1
Contribution to Project: carries out in vivo work

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

(None)