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Award Number: W81XWH-17-1-0373

TITLE: Military Exposure-Related Pleural Mesothelioma: An Innovative Translational Approach to Inform Novel Molecular-Targeted Treatment Development

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CONTRACTING ORGANIZATION: Brigham & Women's Hospital
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6. AUTHOR(S)

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

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

U.S. Army Medical Research and Materiel Command
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Not

14. ABSTRACT

Malignant pleural mesothelioma (MPM) is a highly aggressive form of cancer that develops within the pleural lining of the lungs. Asbestos-related malignancies dropped precipitously in military/veteran populations upon the removal of asbestos from naval ship construction. However, older naval vessels and military facilities still containing asbestos were still in use decades later, resulting in thousands of veterans suffering asbestos exposure. Indeed, it is estimated that military veterans account for one third of all MPM patients. Despite this estimation, there is little data on the phenotype of military exposure and MPM pathogenesis. We recently defined the mutational landscape of MPM and have identified the most commonly mutated genes as BAP1, NF2, TP53, and SETD2, as well as other frequent mutations. We have also classified MPM into 4 distinct molecular clusters that provide new opportunities to identify MPM patients with better prognosis as well as to rationally divide tumors based on distinct molecular/biochemical driving mechanisms.

15. SUBJECT TERMS
Malignant pleural mesothelioma (MPM)

16. SECURITY CLASSIFICATION OF: Unclassified			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.*

Malignant pleural mesothelioma (MPM) is a highly aggressive form of cancer that develops within the pleural lining of the lungs. Asbestos-related malignancies dropped precipitously in military/veteran populations upon the removal of asbestos from naval ship construction. However, older naval vessels and military facilities still containing asbestos were still in use decades later, resulting in thousands of veterans suffering asbestos exposure. Indeed, it is estimated that military veterans account for one third of all MPM patients. Despite this estimation, there is little data on the phenotype of military exposure and MPM pathogenesis. We recently defined the mutational landscape of MPM and have identified the most commonly mutated genes as BAP1, NF2, TP53, and SETD2, as well as other frequent mutations. We have also classified MPM into 4 distinct molecular clusters that provide new opportunities to identify MPM patients with better prognosis as well as to rationally divide tumors based on distinct molecular/biochemical driving mechanisms. The objective of the study is to refine the classification of MPM into biologically and prognostically distinct sub-groups, relate these sub-groups to the military-exposed veterans and rationally design potential biomarker-selected targeted therapies for the military/veteran population for future human trials. This study aims to define and compare MPM tumors from military versus non-military cases for diagnosis and prognosis, using the type of mutations and cluster membership by RNA expression. This study also intends to identify potential novel therapies utilizing genetically-engineered mouse models (GEMMs) to interrogate MPM specific tumorigenesis, invasion, and metastasis. Finally, this study plans to translate potential molecular targets into therapeutics using an *in-vivo* PDXs model. MPM tumors from civilian and military/veteran patients will be genotyped for the five most frequently mutated genes in MPM and will then be used to establish the distribution of mutations of all types in the 4 molecular cluster groups that have been classified. Frequently observed mutations or other genomic aberrations will be further interrogated using GEMMs to more completely understand MPM carcinogenesis and progression, as well as to identify potential targets for therapy. PDXs models will then be developed *in vivo* from the diagnostic/prognostic biomarkers that are identified in the civilian and military populations to focus pre-clinical therapeutics on the two extreme sub-types of MPM: 1 and 4.

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

Malignant pleural mesothelioma (MPM)
genetically-engineered mouse models (GEMMs)
patient-derived xenograft (PDX)

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.

A. Establish Consortium Collaborative Infrastructure (Responsible PI, Harpole-Duke)
   Expected:1-3 months
   Actual: 100% complete

B. Perform RNA-seq analyses on the prospectively-collected, fresh-frozen MPM tumors (Responsible PI, Bueno-BWH)
   Expected: 3-9 months
   Actual: 90% complete. We expect the analysis of the data for validation by December 2019.

C. Investigate whether there are any genomic / genetic differences between civilian and veteran MPM tumors based on the consensus cluster expression and mutational genotyping (N=250 FFPE) (Responsible PI, Bueno-BWH)
   Expected: 6-18 months
   Actual: 50% complete. We are in the process of gene expression analysis of 250 non-military and 250 military exposure mesothelioma cases. Expression analysis for validation is expected to be completed and analyzed by January 2020. BAP1 IHC and NF2 FISH are completed and the database is currently being annotated. We explored DDX3 and SETD2 expression with multiple available antibodies, but they gave poor results. Additional antibodies are currently being tested. We have slides ready from all the specimens and once the best antibodies are chosen these will also be stained and annotated.

D. Identification of Novel Therapies (Responsible PI, Harpole-Duke)
   Expected: 12-24 months
   Actual: In Progress, pending development of 10 PDX models.

E. To translate potential molecular targets into therapeutics using an in-vivo PDX model (Responsible PI, Harpole-Duke) - 10% complete
   Expected completion: 24-36 months
   Actual completion: Pending

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.

A. Establish Consortium Collaborative Infrastructure

This major goal was previously completed and reported in prior reports. There was nothing further to complete regarding this major goal. However, we are pleased to inform the DOD that we have successfully assembled the most comprehensive and largest collection of Mesothelioma cases and associated fresh Frozen and FFPE specimens with linked military service and clinical data in North America. This number is slightly above the one proposed in the grant, to allow for redundancy in case some of the specimens are not adequate.

B. Perform RNA-seq analyses on the prospectively-collected, fresh-frozen MPM tumors.

We have identified statistically robust candidate gene tests for clusters 1 and 4 to have validated with 192 EPP cohort and translated into FFPE with the 250 non-military cases. We have identified statistically robust candidate gene tests for clusters 1 and 4 to have validated with 192 EPP cohort and translated into FFPE with the 250 non-military cases. We have also identified candidate gene tests for clusters 2 and 3; however, through this analysis and other work we have determined that clusters 2 & 3 represent threshold groups that exist on a continuum of EMT between the more robust clusters 1 and 4. For this reason, we are working on a framework to characterize cluster 2 and 3 samples in terms of the more robust clusters 1 and 4, which will be completed by October. Independently we found that the expression of the gene RERG is related to cluster membership and will use that in parallel to assess in the cohorts.

We have assembled 192 cases representing EPP patients. We've obtained gene expression data from 90 of them and prepared RNA from the remaining 102 which is being sent to a contract site for expression analysis to expedite the process and ensure uniformity. We expect the data to be analyzed for validation by December. We also have the matching FFPE blocks pulled and available for this cohort as we are actively working to transfer the winning signatures.

We've identified from our Mesothelioma cases 402 non-military and pulled 265 to confirm a final total of 250. RNA is already made from 102 and ready for analysis, and we are in the process of preparing RNA from the other 163.

C. Investigate whether there are any genomic / genetic differences between civilian and veteran MPM tumors based on the consensus cluster expression and mutational genotyping (N=250 FFPE)

Between BWH and Duke we have assembled 250 FFPE samples from patients with Military exposure. We are preparing those FFPE samples for expression analysis which will be accomplished once the validation tests for transfer to FFPE have been completed. BAP1 IHC and NF2 FISH are completed and the database is currently being annotated. We explored DDX3 and SETD2 expression with multiple available antibodies, but they gave poor results. Additional antibodies are currently being tested by our core. We have slides ready from all the specimens and once the best antibodies are chosen these will also be stained and annotated.

D. Identification of Novel Therapies

In order to identify the role of selected genes in the onset and development of mesothelioma, we are currently making single and compound knock-out mice of NF2, p53 and CDKN2a specifically in mesothelial cells by crossing Wt1-CreER (promoter in mesothelial cells) to p53 fl/fl, NF2 fl/fl and CDKN2a fl/fl mice. The UCSD group has started breeding these knockout mice to make single and compound knock-out mice of NF2, p53 and CDKN2a specifically in mesothelial cells by crossing Wt1-CreER (promoter in mesothelial cells) to p53 fl/fl, NF2 fl/fl and CDKN2a fl/fl mice. Once these single [Wt1-CreER; p53 fl/fl, Wt1-CreER; NF2 fl/fl and Wt1-CreER; CDKN2a fl/fl] and compound knock out [(Wt1-CreER; NF2 fl/fl; p53 fl/fl), (Wt1-CreER; NF2 fl/fl; CDKN2a fl/fl) (Wt1-CreER; NF2 fl/fl; p53 fl/fl; CDKN2a fl/fl)] mice were obtained, they were administered tamoxifen at 6 weeks of age to activate cre-mediated knockdown of these genes in the mesothelial region of lung. These mice will be harvested at 40 weeks post tamoxifen administration. We are currently waiting this 40 weeks' time-point to finish. Post 40 weeks, mice will be sacrificed, and lungs will be harvested. Lung and pleural surfaces will be analyzed for tumors. This strategy will assist us to not only investigate the individual effect of genes like NF2, p53 and CDKN2a but also let us compare the effect of multiple gene knockouts [(NF2+p53) (NF2+CDKN2A) (NF2+p53+CDKN2A)] on mesothelioma onset and progression.

Additionally, we are also breeding WT1-CreER; Cas9; FGFP mice, to which lentiviral particles would be injected. We are currently making sgRNA lentiviral particles for NF2, p53 and CDKN2a using 293 FT cell line in the lab.

In order to identify the novel therapies for malignant mesothelioma, we will be testing library of small molecule inhibitors and FDA approved drugs on normal and oncogenic mesothelial cells in vitro. For this the first step is to isolate and then grow these mesothelial cells in culture. We have optimized the procedure to isolate normal and tumor cells from normal and knockout mice respectively. In addition to this, we are currently standardizing the procedure to grow normal and tumor cells in 3D cultures in vitro.

E. To translate potential molecular targets into therapeutics using an in-vivo PDX model. To date, BWH reports that Nine PDX models have completed through passage 0 into passage 1; 5 Biphasic, 3 epithelioid, 1 sarcomatoid. Three additional PDX models are in p0 and will soon be ready for p1 passage. Four of the nine completed models have been sent to Duke's animal facility to begin therapeutic agent testing. As of Aug 20, 2019, Duke has implanted a total of 13 MPM tumors in mice (a total of 2 freshly isolated and 11 cryopreserved). One mouse with implanted sarcomatoid tumor died shortly after the tumor became fixed; tumor from the same source patient has been implanted in a new mouse. Another mouse was euthanized due to excessive weight loss and immobility, though the implanted tumor had not grown on necropsy.

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."

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.

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.

A. Establish Consortium Collaborative Infrastructure: maintain the established consortium infrastructure

B. Perform RNA-seq analyses on the prospectively-collected, fresh-frozen MPM tumors. Continue to work on a framework to characterize cluster 2 and 3 samples in terms of the more robust clusters 1 and 4. We will further assess the gene RERG as it relates to cluster membership. Complete the gene expression analysis for validation by December and work to transfer the winning signatures to matched FFPE blocks.

   We've identified from our Mesothelioma cases 402 non-military and pulled 265 to confirm a final total of 250. RNA is already made from 102 and ready for analysis, and we will continue to prepare RNA from the other 163. We plan to complete the expression analysis for validation by January 2020. We're also preparing the matching FFPE samples (which we have) for expression analysis which will be completed in the Spring after confirming the proposed tests.

C. Investigate whether there are any genomic / genetic differences between civilian and veteran MPM tumors based on the consensus cluster expression and mutational genotyping (N=250 FFPE)

   Between BWH and Duke we have assembled 250 FFPE samples from patients with Military exposure. We're preparing those FFPE samples for expression analysis which will be accomplished once the validation tests for transfer to FFPE have been completed. We anticipate completion by the end of the funding year. We will continue to annotate the database for BAP1 IHC and NF2 FISH. We will continue to test additional antibodies for DDX3 and SETD2 expression We have slides ready from all the specimens and once the best antibodies are chosen these will also be stained and annotated.

D. Identification of Novel Therapies

   We will continue to breed single and compound knock-out mice of NF2, p53 and CDKN2a by crossing Wt1-CreER (promoter in mesothelial cells) to p53 fl/fl, NF2 fl/fl and CDKN2a fl/fl mice and continue the breeding ofvWT1-CreER; Cas9; FGFP mice, to which lentiviral particles would be injected. We will continue making sgRNA lentiviral particles for NF2, p53 and CDKN2a using 293 FT cell line in the lab.

In addition to this, we will complete the standardization of the procedure to grow normal and tumor cells in 3D cultures in vitro.

E. To translate potential molecular targets into therapeutics using an in-vivo PDX model.

We intend to continue generating PDX new PDXs and continue the passage of the models we currently have.

4. **IMPACT:** D*escribe 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).

We have assembled the most comprehensive and largest collection of Mesothelioma cases and associated fresh Frozen and FFPE specimens with linked military service and clinical data in North America, available for current and future analyses. This comprehensive proposal for molecular characterization of mesothelioma whose goal is identification of novel targeted therapies specifically matched with genetically-identified subsets of tumors study, seeks to identify genetic markers specific to military-related MPM. Thus, these findings will be relevant to thousands of military veterans who were exposed to asbestos. The identification of these markers could lead to earlier/enhanced diagnosis and treatment strategies for veterans afflicted with this deadly disease, and improve patient survival.

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.

Nothing to Report

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.

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.

Cluster-4 Mesothelioma tumors are very rare, therefore we may not reach the stated goal of five Cluster-4 PDX models within this three year grant period.

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.

Nothing to report

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

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

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."*

- **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).*

  Nothing to Report

  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).*

  Nothing to Report

  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.*

  Nothing to Report

- **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.

  Nothing to Report

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

  Nothing to Report

- **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.

  Nothing to report

- **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.*

    A. Collaborative mesothelioma clinical RedCAP database

    B. Collaborative Biospecimen collection of fresh-frozen and FFPE mesothelioma tumor samples – samples are continuing to be added as the project progresses

    C. Collaborative data repository of RNA-seq analyses on mesothelioma tumor samples – data is continuing to be added as analyses are completed

    D. - Database of clinical data, outcomes, and military exposure on 500 patients.

E. - Physical collection of 250 fresh frozen non-military and matching FFPE samples, plus 250 Military FFPE samples.
F. - >10 PDX Mesothelioma mouse models.
G. - Molecular signatures of potential clinical value

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.)*

Name: Mary N Dao (BWH)
Project Role: Technician
Nearest person month worked: 2
Contribution to Project: Performing technical effort in preparing samples for analysis
Funding Support: DoD W81XWH-17-1-0372

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.*

Independent reports will be submitted by BOTH the Initiating PI and the Collaborating/Partnering PI.

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.*

Not Applicable