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TITLE: *Targeting Satellite Repeat RNAs in High-Grade Serous Ovarian Cancer*

PRINCIPAL INVESTIGATOR: Rebecca L. Porter, MD, PhD

CONTRACTING ORGANIZATION: The General Hospital Corporation dba Massachusetts General Hospital

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13. SUPPLEMENTARY NOTES

14. ABSTRACT: There is a critical need for novel therapeutic strategies in HGSOC, specifically for platinum-resistant disease. Recent work from our lab and others has discovered aberrant expression of repeat non-coding RNAs across many cancers, and these repeat RNAs have active reverse transcription (RT) and expansion in cancer genomes, are recognized by pathogen recognition receptors and can trigger cancer cell death and alterations in the immune microenvironment. Thus, the goals of this project to 1) define the spectrum of repeat RNAs expressed across epithelial ovarian cancers and link these to immune characteristics of the tumor and response to therapies and 2) target repeat RNA reverse transcription as a potential therapeutic strategy in HGSOC. To date, Total RNASeq was performed on 32 patient-derived ovarian cancer cell lines, 11 HGSOC PDX, 11 additional ovarian cancer cell lines, revealing abundant repeat RNA expression from all three major subclasses. Comparison of repeatome data from HGSOC models with previously generated RNA-seq data from colorectal cancer and pancreatic ductal adenocarcinoma models shows that repeat RNA profiles are unique across epithelial cancers. In HGSOC models, we find SAT and HERV repeats display the most variable expression. In particular, HSATII, a cancer specific satellite, is strongly expressed in HGSOC and displays highly variable expression across different models. Preliminary data targeting HSATII RNA levels shows cytotoxicity in some HGSOC cell lines, and combinatorial therapies are currently being investigated in vitro and in vivo using xenograft models.

15. SUBJECT TERMS:
NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Although the majority of women with HGSOC will enter remission following cytoreductive surgery and platinum-based chemotherapy, most experience disease relapse and ultimately die from increasingly platinum- and treatment-resistant disease. More recently, poly ADP ribose polymerase inhibitors (PARPi) and immune-based therapies have been and are continuing to be explored as additional therapies in HGSOC. However, PARPi are less effective in platinum-resistant disease, and the immunosuppressive tumor microenvironment (TME) has limited the activity of immunotherapies in HGSOC to date. Thus, there is a critical need for novel therapeutic strategies in HGSOC, specifically for platinum-resistant disease. Recent work from our lab and others has discovered aberrant expression of repeat non-coding RNAs across many cancers, and these repeat RNAs are now known to behave like viruses with active reverse transcription (RT) and expansion in cancer genomes, and they are recognized by pathogen recognition receptors, triggering cancer cell death and alterations in the immune tumor microenvironment. Given this, the overall goals of this project are two-fold to 1) define the spectrum of repeat RNAs expressed across epithelial ovarian cancers and link these to immune characteristics of the tumor and response to therapies and 2) target repeat RNA reverse transcription as a potential therapeutic strategy in high grade serous ovarian cancer.

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

high grade serous ovarian cancer, repeat non-coding RNAs, satellite repeats, reverse transcription, tumor immune microenvironment

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.

Major Task 1: Quantify repeat RNAs in HGSOC cell lines and PDX models – months 1-6
- 100% completed
- Actual completion date: Sept 2019

Major Task 2: Perform RNA-ISH/IHC on Epithelial Ovarian Cancer (EOC) TMAs – months 0-12
- 90% completed

Major Task 3: Exosome isolation and RNA-seq of exosomes – months 9-12
- 25% completed

Major Task 4: Inhibit repeat RNA RT with NRTIs in HGSOC cell lines and PDX models – months 12-15
- 75% completed

Major Task 5: Evaluate response to NRTI therapy in xenograft tumors – months 15-24
- 15% completed

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.

Specific Aim 1: Define the expression of non-coding repeat RNAs in HGSOC cell lines and human tumors using total RNA-sequencing

Major Task 1: Quantify repeat RNAs in HGSOC cell lines and PDX models

Major Activities: We have utilized our Total RNASeq platform and novel computational pipelines to quantify the repeatome in HGSOC model systems. To date, Total RNASeq has been performed on 32 patient-derived ovarian cancer cell lines, 11 HGSOC PDX, 11 additional ovarian cancer cell lines and several fallopian tube epithelial cell lines as normal controls.

Key outcomes: Overall, we detect abundant repeat RNA expression from all three major subclasses, endogenous retroviruses (HERV), and satellites (**Fig. 1A; see appendix**). Comparison of repeatome data from EOC models with previously generated RNA-seq data from colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC) preclinical models reveals that repeat RNA profiles are unique across epithelial cancers and repeat RNA profiles can be used to cluster these models by cancer type (**Fig. 1B**). Across HGSOC models, we find variable expression of each subclass of repeats, with SAT and HERV displaying the most variable expression (**Fig. 1C**). In particular, *Human satellite II* (HSATII), a cancer specific satellite, is strongly expressed in HGSOC and displays highly variable expression across different models (**Fig. 1A**).

Major Task 2: Perform RNA-ISH/IHC on Epithelial Ovarian Cancer (EOC) TMAs

Major Activities: We selected repeat RNAs from three distinct subsets that demonstrated high and/or variable expression in our preclinical models for validation in human tumors. Therefore, we obtained RNA-ISH probes complimentary to HSATII (SAT), HERV-H (ERV) and LINE-1 (retrotransposon) sequences and applied them to a tissue microarray (TMA) of >150 cases of human epithelial ovarian cancers using RNA-in situ hybridization (RNA-ISH). In addition, the TMA was stained with antibodies to CD8 and CD163 to quantify cytotoxic T cells and tumor-associated macrophages, respectively. RNA and protein signal was quantified using digital image analysis on the Halo software (Indica Labs).

Key outcomes: These experiments confirmed that repeat RNAs are indeed expressed in human EOC and their expression levels vary from patient to patient (**Fig 2**). Combined RNA-ISH and immunohistochemistry for cytotoxic T cells and tumor-associated macrophages are currently being analyzed to identify any correlations between repeat RNA expression levels with immune cell infiltrates in the tumor. We are also actively investigating the relationship between repeat RNA expression and clinical outcomes using available clinical data from tumors included in the TMA.

Major Task 3: Exosome isolation and RNA-seq of exosomes

Major Activities: We have isolated extracellular vesicles (EVs) from 4 HGSOC cell lines by collecting supernatant from 3D cultures and performing standard filtering and ultracentrifugation procedures. Total RNA was purified from the collected EVs and has been stored for later RNA-seq analysis.

Specific Aim 2: Test the effect of repeat RNA RT inhibition as a therapeutic strategy in HGSOC
Major Task 4: Inhibit repeat RNA RT with NRTIs in HGSOC cell lines and PDX
Major Task 5: Evaluate response to NRTI therapy in xenograft tumors
Major Activities and Key Outcomes: In Aim 2, we hypothesized that targeting repeat RNA reverse transcription using NRTIs may be an effective therapeutic strategy in EOC. Thus, we treated a panel of EOC cell lines with a selection of NRTIs *in vitro* and tested cytotoxicity and effect on repeat RNA expression. None of the NRTIs that were tested have demonstrated cytotoxicity as a single agent in EOC cell lines. Next, we tested NRTIs combined with epigenetic therapies (azacytidine and HDAC inhibitor) and cytotoxic chemotherapy (carboplatin and paclitaxel). While chemotherapy agents and HDAC inhibitors demonstrate single-agent cytotoxicity in the majority of EOC cell lines, no additive or synergistic activity was observed when combined with NRTIs, suggesting that NRTIs are likely not effective in EOC models, at least as single agents or in the combinations we have tested. Given this, we are now attempting to target satellite repeat RNA reverse transcription using locked nucleic acids (LNAs). We chose to focus first on HSATII, given its known immunomodulatory properties and its variable expression across different EOC models, providing a system in which to study cell lines with high and low HSATII expression. Significant cytotoxicity was observed in several cell lines transfected with LNAs designed specifically to target *HSATII* RNA (**Fig. 3A**). RNA-Seq results show that LNA increases HSATII RNA levels early after transfection ((**Fig. 3B**), suggesting that increased SAT RNA may be toxic to EOC cells. Therefore, we are currently investigating the effects of this LNA on other repeat RNA levels in the cell, and are testing the effect of HSATII LNA *in vivo* using xenograft models.

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.

Training: during the first 12 months of this award, I have mentored two different technicians on this project. For each, this has included one-on-one training in areas of cell culture, RNA and DNA isolation, total RNA-sequencing preparation and data analysis, immunohistochemistry, RNA in situ hybridization, digital image analysis, and xenograft generation.

Professional Development: I have attended two conferences during this report period at which I presented our preliminary findings in poster format. These were the AACR Advances in Ovarian Cancer Research Biannual Meeting in Atlanta, GA in Sept 2019 and the Stand Up to Cancer Scientific Summit in Santa Monica, CA in Jan 2020. A third abstract was also chosen for an oral presentation at a local symposium, but this was canceled due to COVID-19.

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.

In the final 12 months of the funding period, we plan to focus on completing Major Tasks 3, 4 and 5. More specifically, we will:

1) Continue to purify EVs from additional HGSOC cell lines and will perform Total RNA-seq on EV RNA to define the expression of repeat RNAs in tumor-derived exosomes. The EV repeatome will then be compared with the parental cell repeatome to identify specific repeat RNAs that may be important in tumor cell communication with the immune microenvironment.

2) Further characterize the cellular response to HSATII-targeted LNA therapy *in vitro* by transfecting additional high- and low-expressing HSATII cell lines with HSATII-specific LNA and assessing changes in expression of relevant repeat RNAs as well as effect on tumorsphere growth and viability.

3) Test combinatorial strategies with LNA + other therapeutic agents including chemotherapy, DNA damage repair pathway inhibitors and epigenetic therapies in preclinical models.

4) Assess the efficacy of satellite RNA-directed LNAs and LNA combinations *in vivo* using murine xenografts. We plan to establish tumors in NSG mice using the xenograft models we have already developed, then treat systemically with LNA or LNA + additional drug and monitor effect on tumor growth rate as well as changes in tumor cell repeat RNA expression and immune cell infiltrates.

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).

The potential impact of a more comprehensive understanding of the "repeatome" in ovarian cancer is twofold. First, characterization of the repeatome would allow for the development of more precise molecular subtyping and/or specific cancer biomarkers, given that some repeat RNAs are specific for cancer cells. Second, the fact that cancer cells reverse transcribe repeat RNAs similar to retroviruses may represent a unique therapeutic opportunity to exploit. Indeed, the data we have generated in the first 12 months of this project confirm abundant and variable expression of repeat RNAs in ovarian cancer and some evidence of cytotoxicity upon modulation of HSATII levels in the cancer cells. Importantly, since work by others in different cancers has demonstrated that repression of repeat RNAs appears to be important in surviving death via cytotoxic agents (Guler et al*., Cancer Cell*, 2017), resistant cells may be particularly vulnerable to this strategy of increasing repeat RNA stress, specifically addressing the critical need for therapies in treatment-resistant disease. Altogether, the proposed work may not only allow for more precise subtyping and/or identification of novel biomarkers for HGSOC, but may also unveil a novel therapeutic strategy to specifically target cancer cells, particularly in the setting of treatment-resistant disease, making them more responsive to current chemotherapies and epigenetic therapies.

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:*

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.

Nothing to report

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.

The COVID-19 pandemic resulted in full shut down of laboratory operations for several weeks of this funding period, which has delayed scientific progress significantly. Data analysis and computational work has continued, but laboratory-based work was halted and will need to be reinstated when it is safe to do so. This has especially impacted the animal experiments and may significantly alter the initially proposed timeframe for achieving each milestone.

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.*

1. **Porter RL,** Szabolcs A, Desai N, Thapar V, Pepin D, Solovyov A, Greenbaum B, Ting DT. Repeatome profiling in high grade serous ovarian cancer reveals abundant repeat non-coding RNA. AACR Advances in Ovarian Cancer Research Biannual Meeting, September 13-16, 2019, Atlanta, GA

2. **Porter RL,** Thapar V, Pepin D, Solovyov A, Szabolcs A, Flores M, Desai N, D, , Greenbaum B, Ting DT. Repeatome profiling in high grade serous ovarian cancer reveals abundant repeat non-coding RNA expression. Stand Up to Cancer Scientific Summit, Santa Monica, CA, Jan 26-28, 2020

- **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.*

Nothing to report

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: *Micayla Flores*
Project Role: *Technician*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *4*

Ms. Flores has performed work in the areas of cell culture, RNA isolation and preparation for RNA-Seq, in vitro drug testing and cytotoxicity assays, and digital image analysis.
Funding Support:

Name: *Neelima KC Magnus*
Project Role: *Technician*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *3*

Ms. Magnus has performed work in the areas of cell culture, RNA isolation and preparation for RNA-Seq, in vitro drug testing and cytotoxicity assays.
Funding Support:

Name: *Rebecca Porter, MD, PhD*
Project Role: *PD/PI*
Researcher Identifier (e.g. ORCID ID): *0000-0002-4848-1275*
Nearest person month worked: *3.96*

Contribution to Project: She has significant experience with human cancer cell culture, molecular biology and mouse models that will be utilized for this project. In addition, she has become familiar with next generation sequencing techniques and the use of branched nucleic acid technologies to detect and quantify repeat RNAs over the past two years of working in the Ting Lab. She will oversee all molecular biology, mouse models, and sequencing library construction for this project. She will provide the training and mentorship for sequencing, cell biology, and mouse models for the research technician. With Dr. David Ting, she will submit and manage all IRB and IACUC protocols for this project. In addition, as a senior Medical Oncology Fellow in the Gynecologic Oncology groups at the Dana Farber Cancer Institute and the MGH Cancer Center, she will be working directly with collaborator, Dr. Ursula Matulonis and will have access to fresh ovarian cancer tumors samples.

Funding Support:

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.*

Organization Name: Memorial Sloan Kettering Cancer Center
Location of Organization: (if foreign location list country) New York, NY
Partner's contribution to the project (identify one or more)
Collaboration: Drs. Benjamin Greenbaum and Alexander Solovyov are long-time collaborators working on RNA-seq projects in PDAC and CRC (Solovyov A et al, Cell Reports, 2018), and have assisted with development of programs to map repetitive elements in the genome.

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.*

Appendix 1: Figures 1-3