AWARD NUMBER: W81XWH-18-1-0590

TITLE: Novel Strategies to Combat Post-Traumatic Osteoarthritis

PRINCIPAL INVESTIGATOR: Constance Chu

CONTRACTING ORGANIZATION: Palo Alto Veterans Institute for Research
Menlo Park, CA 94025

REPORT DATE: September 2019

TYPE OF REPORT: Annual

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

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14. ABSTRACT This program project addresses the overarching clinical need for effective treatments to delay or prevent the development of post-traumatic osteoarthritis (PTOA), a leading cause of disability for military service members and Veterans. The overarching goal is to test the hypothesis that prolonged inflammatory responses to joint injury contribute to progressive cartilage degeneration and subsequent development of PTOA. Consequently, our program project evaluates several innovative strategies to modulate joint inflammation through: [1] cellular and molecular treatments acutely and early after ACL injury in patients and in animal models (Projects 1, 2 and 3), [2] rehabilitation intervention in patients early after ACL reconstruction (ACLR) and prior to OA onset (Project 4), and [3] localized gene therapy for sustained administration of anti-inflammatory therapy in an equine model of PTOA (Project 5). Project 1 will examine the mechanisms by which plasmin and fibrinolysis sustain inflammation and contribute to PTOA. Project 2 will conduct a randomized controlled clinical trial to see whether inhibition of fibrinolysis using tranexamic acid (TXA) acutely after ACL injury reduces inflammation and delays joint degeneration in humans. To address widespread interest in the use of stem cells in the treatment and prevention of OA, Project 3 will evaluate the anti-inflammatory and disease-modifying effects of induced pluripotent stem cell (iPSC)-derived “rejuvenated” human MSC from ACL injured patients. Project 4 will integrate the use of novel quantitative (qMRI) MRI UTE-T2* mapping to evaluate whether an innovative active feedback gait retraining program can reduce both inflammatory and structural markers of elevated OA risk after ACLR. Finally, Project 5 will evaluate the effects of intra-articular anti-inflammatory gene therapy to prevent PTOA. This multidisciplinary program aims to reduce the disease burden of PTOA.
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Project 1

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<td>Principal Investigator Name:</td>
<td>Constance R. Chu, MD</td>
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<tr>
<td>Principal Investigator Organization and Address:</td>
<td>VA Palo Alto Health Care System/PAVIR 3801 Miranda Ave Palo Alto, CA 94304-1290</td>
</tr>
<tr>
<td>Principal Investigator Phone and Email:</td>
<td>(650) 721-7618 <a href="mailto:chucri@stanford.edu">chucri@stanford.edu</a></td>
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Email the report and any other attachments to the Grants Officer’s Representative (GOR) and Grants Specialist at the email addresses specified in the award document. Name the file with the award number, followed by “QtrlyTechProgReport Month Year.”

If you have questions, contact the GOR.
1. ACCOMPLISHMENTS: THE PI IS REMINDED THAT THE RECIPIENT ORGANIZATION IS REQUIRED TO OBTAIN PRIOR WRITTEN APPROVAL FROM THE AWARDING AGENCY GRANTS OFFICER 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.

Project 1: The Role of Plasmin in Post-Traumatic Osteoarthritis: This project will examine the hypothesis that deregulation of the fibrinolysis system drives the pathogenesis of PTOA by promoting inflammation and cartilage degradation.

Aim 1: Major Task 1: Subtask 1: ELISA and Luminex assays on the ACLT and DMT cohorts (months 1-6)

Aim 2: Major Task 1: Subtask 1: MMLT or MMLT& ACLT surgery and tranexamic acid treatment on mice (months 1-6)

Aim 3: Major Task 1: Subtask 1: Design and perform Regimen 1 tranexamic acid treatment on mice subjected to MMLT or MMLT&ACLT (months 1-6)

What was accomplished under these goals?
For this quarterly reporting period only 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.

Aim 1: Major Task 1: Subtask 1: ELISA and Luminex assays on banked samples from ACLT, DMT and OA cohorts. (months 1-6) Further ELISA and Luminex analyses were performed on knee synovial fluids from ACLT, DMT, as well as OA comparators to measure cytokines and other immune mediators. Significance analysis of microarrays (SAM) was used to identify cytokine and immune mediators that were statistically different in their levels between OA, DMT and ACLT, and the cytokines and immune mediators exhibiting statistical differences were displayed in heatmaps. In our first progress report, we described upregulation of type II cytokines in human OA, suggesting that type II immunity may play a role in promoting progression to OA following ACLT. In the prior period, we analyzed additional OA, ACLT, for cytokines, chemokines, and other secreted molecules and observe a clustering pattern that suggests approximately 4 distinct molecular subgroups, each characterized by dysregulation of distinct sets of cytokines and chemokines. Further analyses were performed in the current reporting period (Figure below).
TOTAL PROTOCOLS: State the total number of human use protocols required to complete this project (e.g., 5 human subject research protocols will be required to complete the Statement of Work.”). If not applicable, write “No human subjects research will be performed to complete the Statement of Work.”

PROTOCOL(S): List the identifier and title for all human use protocols needed to complete the project. Include information about the approved target number for clinical significance, type of submission, type of approval with associated dates, and performance status.

The following format shall be used:

Protocol (of total):
Protocol [HRPO Assigned Number]:
Title:
Target required for clinical significance:
Submitted to and Approved by:

STATUS:
(i) Number of subjects recruited/original planned target:
Number of subjects screened/original planned target:
Number of patients enrolled/original planned target:
Number of patients completed/original planned target:

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

TOTAL PROTOCOLS: 0
(b) Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training

“Cadaver” is defined as a deceased person or portion thereof, and is synonymous with the terms “human cadaver” and “post-mortem human subject” or “PMHS.” The term includes organs, tissues, eyes, bones, arteries or other specimens obtained from an individual upon or after death. The term “cadaver” does not include portions of an individual person, such as organs, tissue or blood, that were removed while the individual was alive (for example, if a living person donated tissue for use in future research protocols, that tissue is not considered a “cadaver” under this policy, regardless of whether the donor is living or deceased at the time of tissue use).

**TOTAL ACTIVITIES:** State the total number of RDT&E, education or training activities that will involve cadavers. If not applicable, write “No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).”

**ACTIVITIES:** Provide the following information in a bulleted list for all RDT&E, education or training activities involving human cadavers conducted or supported during the quarter:

- Title of the RDT&E, education or training activity
- SOW task/aim associated with the activity
- Date the activity was conducted
- Identification of the organization’s responsible individual (e.g., PI or individual primarily responsible for the activity’s conduct)
- Brief description of the use(s) of cadavers in the activity and the total number of cadavers used during the reporting period
- Brief description of the Department of Army organization’s involvement in the activity
- Status of document submission and approvals
- Problems encountered in the procurement, inventory, use, storage, transfer, transportation and disposition of cadavers used for RDT&E, education or training. Examples of problems include but are not limited to: loss of confidentiality of cadaveric donors, breach of security, significant deviation from the approved protocol, failure to comply with state laws and/or institutional policies and public relations issues.

**TOTAL ACTIVITIES:** “No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).”

**ACTIVITIES:** No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).

(c) Animal Use Regulatory Protocols

**TOTAL PROTOCOL(S):** 1

State the total number of animal use protocols required to complete this project (e.g., 2 animal use research protocols will be required to complete the Statement of Work.). If not applicable, write “No animal use research will be performed to complete the Statement of Work.”

**PROTOCOL(S):**

List the identifier and title for all animal use protocols needed to complete the project. Include information about the approved target number for statistical significance, type of submission, type of approval with associated dates, and performance status.

The following format shall be used:

**Protocol (1 of 1 total):**

- Protocol [ACURO Assigned Number]: ROW1749
- Title: The Role of Plasmin in Post-Traumatic Osteoarthritis
- Target required for statistical significance: \( n = 8 \) per experimental arm
- Target approved for statistical significance: \( n = 10 \) per experimental arm
Submitted to and Approved by:
Provide bullet point list of protocol development, submission, amendments, and approvals (include IACUC in addition to ACURO).

- Initial submission May 4th, 2018;
- Approval date May 22nd, 2018
- Amendment to address comments by DoD: Submitted March 11th, 2019 excepted Approval March 26th 2019.
- Approval date May 30, 2019 (APLAC ROW1749)

Status:
Provide bullet point list of performance and/or progress status relating to the above protocol and discuss any administrative, technical, or logistical issues that may impact performance or progress of the study (e.g. animal use protocol needs revision to minimize animal suffering, animal protocol modification to include additional staff) for the above ACURO approved protocol.

While we obtained the local IACUC approval on May 22nd 2018, as we waited for the DoD IACUCC approval, no work has been done under this protocol. Last amendment submitted on March 11th 2019 addressed the clarification question by the DoD committee and we also removed two personal (Nick Hu and Eileen Elliott) who left our team.

TOTAL PROTOCOL(S): 1

PROTOCOL (1 of 1 total):
Protocol [ACURO Assigned Number]: Log #PR171647.e001 (Pending approval)
Title: The Role of Plasmin in Post-Traumatic Osteoarthritis

Target required for statistical significance: n = 8
Target approved for statistical significance: n = 10

SUBMITTED TO AND APPROVED BY:
- VA Palo Alto IACUC initial submission May 4th, 2018;
- Approval date May 22nd, 2018
- Amendment to add personal Submitted Oct 17th, 2018; Approved Oct 18, 2018.
- Amendment to address comments by DoD: Submitted March 11th, 2019; anticipated approval March 26th 2019.

STATUS:
- The rodent studies of Projects 1 received VA Palo Alto IACUC approval and were submitted to ACURO for review.
- Comments for clarification from ACURO received on March 6th 2019, and responses submitted and being reviewed by VA Palo Alto IACUC with anticipated approval date of March 26, 2019.
- Full approval received May 30, 2019 (APLAC protocol ROW1749)

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

In the next reporting period we will perform the following:

Aim 1: Major Task 1: Subtask 1: ELISA and Luminex assays on the ACLT and DMT cohorts (months 1-6). We will perform additional informatics analysis of the ELISA and Luminex assays on ACLT, DMT, and OA patient knee synovial fluid and serum samples, as well as perform additional bioinformatics analyses and displays of the resulting datasets. We will perform further ELISA and Luminex analyses on samples collected as part of the clinical trial, once available, and classify patients based on our results obtained to date.

Aim 2: Major Task 1: Subtask 1: MMLT or MMLT & ACLT surgery and tranexamic acid treatment on mice (months 1-6). Our animal protocols are now approved. The first mouse experiment has been initiated, and mice received treatment with tranexamic acid for different periods, and results are anticipated next Quarter.

Aim 3: Major Task 1: Subtask 1: Design and perform Regimen 1 tranexamic acid treatment on mice subjected to MMLT or MMLT & ACLT (months 1-6). These treatment experiments were designed, and following approval of our animal protocol the first mouse experiment was initiated, and mice received treatment with tranexamic acid for different periods, and results are anticipated next Quarter.

- publications, conference papers, and presentations;
- website(s) or other Internet site(s);
- technologies or techniques;
- inventions, patent applications, and/or licenses; and
- other products, such as data or databases, biospecimen collections, germplasm, audio or video products, software, models, educational aids or curricula, instruments or equipment, data and research material, clinical or educational interventions, or new business creation.

Nothing to report

3. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) Project Directors (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).

Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person worked on the project for any significant length of time. For example, if an undergraduate student graduated, entered graduate school, and continued to work on the project, show that person as a graduate student, preferably explaining the change in involvement.

Describe how this person contributed to the project. 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.
4. CHANGES/PROBLEMS: THE PD/PI IS REMINDED THAT THE RECIPIENT ORGANIZATION IS REQUIRED TO OBTAIN PRIOR WRITTEN APPROVAL FROM THE AWARDING AGENCY GRANTS OFFICER 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:

a. Actual Problems or delays and actions to resolve them
Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. Also 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.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, discuss any problems or barriers encountered, if applicable, and what has been done to mitigate those issues. Discussion may highlight enrollment problems, retention problems, and actions taken to increase enrollment and/or improve retention.

Nothing to Report

b. Anticipated Problems/Issues
Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

Delays in approval of animal protocols have delayed initiation of the mouse studies. Animal protocols were approved May 30, 2019 and the first mouse experiments have now been initiated.
5. SPECIAL REPORTING REQUIREMENTS:

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

Not applicable.
Anterior cruciate ligament tear (ACLT) is a common knee injury in young active people, and occurs 10 times more frequently in military service members. The injury also leads to PTOA in roughly half of patients about ten years after injury. Intra-articular bleeding accompanies joint trauma, and is a hallmark of ACLT. There is an increasing body of evidence showing that dysregulation of plasmin mediated fibrinolysis by joint bleeding contributes to persistent low-grade inflammation. Fibrinolysis has been associated with the inflammatory processes that have been shown to play a central role in OA pathogenesis. Tranexamic Acid (TXA), an inexpensive fibrinolysis inhibitor routinely used to reduce blood loss in orthopedic surgery may arrest PTOA. We therefore propose an early Phase II double blind randomized controlled trial (RCT) to test the hypothesis that TXA treatment acutely after joint injury will reduce synovial fluid markers of inflammation and cartilage degradation and will improve patient reported outcomes (PROs) and cartilage subsurface matrix structure assessed by quantitative magnetic resonance imaging (qMRI) ultrashort echo-time enhanced T2* (UTE-T2*) mapping 6 months and 2 years after ACL reconstruction (ACLR).
2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

1. Osteoarthritis (OA)
2. Post-traumatic OA
3. Anterior Cruciate Ligament (ACL)
4. ACL reconstruction (ACLR)
5. Inflammation
6. Plasmin
7. Fibrinolysis
8. Randomized Clinical Trial (RCT)
9. Tranexamic Acid (TXA)
10. Quantitative Magnetic Resonance Imaging (qMRI)
11. Ultrashort echo-time T2* mapping (UTE-T2* mapping)
12. Patient Reported Outcomes (PROs)

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.

Although no subjects have yet been recruited at either site (Stanford or TRIA), both sites are now open to recruitment.

Efforts in this first year of the study focused on start-up activities including receiving all necessary regulatory approvals to perform the proposed studies. Initial IRB and HRPO approvals, as well as IRB and HRPO annual continuing renewals were been granted to both Stanford University and to TRIA Research Institute for the proposed protocols. Significantly, IND exemption for proposed tranexamic acid dosing was granted by the FDA. Data Use Agreement and material transfer agreements between TRIA and Stanford were fully executed to permit the sharing of MRI sequences and study patient data. MRI research agreements were been established between GE Healthcare and both study sites. Required MRI hardware and software was secured and tested at both sites. A RedCap platform for data capture and archiving specifically designed and built for this study was distributed to both sites.

Efforts have also focused on developing medication distribution systems between the collaborating pharmacy to local sites and also determining appropriately blinded medication distribution systems within each local site. The randomization scheme was finalized and procedures have been implemented for distribution of oral medications at both sites.

Significant effort has been spent on developing patient recruitment materials and procedures. A total of 7 Stanford Orthopaedic surgeons have agreed and have received local IRB approval to participate in patient referral, recruitment and study procedures. Stanford Emergency Department clinicians have also agreed and received IRB approval to assist with subject referral. In addition, study staff will be automatically alerted through a system of automatics texts to patients presenting in Stanford Hospital Emergency departments with traumatic knee injury. These texts will allow study staff to assist patients who may have an acute ACL tear with getting a same-day appointment with a Stanford Orthopaedic clinician. Efforts are underway to establish similarly stream-lined referral systems with Stanford athletic departments. Marketing media and recruitment strategies to further facilitate subject recruitment are under development with the Stanford Health Care Marketing Strategy Office.

Research efforts were delayed in the first year of the study due to delays in completing the Stanford and TRIA subcontracts. MRI testing was delayed as the TRIA site underwent a manufacturer-initiated MRI scanner software update; however, study MRI protocols were successfully re-installed following the update.
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.

### Major Tasks:

#### 1. Study Start Up
- Milestone #1: IRB and HRPO approval received for both sites
- Milestone #2: Subcontract & DUA between coordinating center and sites fully executed
- Milestone #3: MRI agreements and protocols established and tested at both sites
- Milestone #4: Randomization Scheme and procedures for TXA/placebo distribution determined for both sites
- Milestone #5: Site Initiation Visit?

  Standard Operations Protocol, 90% complete. IV dosage chain of custody tbd.
  RedCap data capture system built, tested and deployed to both sites.
  Investigator meeting & training protocol?

#### 2. Subject Recruitment
- Both sites (Stanford and TRIA) are now open to recruiting subjects.
- Additional personnel, including a Clinical Research Coordinator and also a CRC associate have been hired to facilitate the study.
- Recruitment materials, including ads & brochures, have been distributed to offices and study personnel of referring physicians and departments.
- Stanford Hospital Emergency Department clinicians, and a total of 7 Stanford Orthopaedic clinicians have been added as study personnel to assist with subject referral, recruitment and study procedures.
- Marketing media and recruitment strategies to facilitate subject recruitment are under development with the Stanford Health Care Marketing Strategy Office.

#### 3. Clinical Monitoring & Quality Control Procedures –
- Data Safety Monitoring Board has been established.

#### 4. Subject Follow-Up
- NA

#### 5. Study Governance
- Yr 1 Annual Investigator meeting conducted Oct. 19, 2018
- Yr 2 Annual Investigator meeting planned for Oct. 25, 2019

#### 6. Analyze and Disseminate Results
- NA

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 plan to enroll patients at both sites.

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).

Nothing to report

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.

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**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.

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**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.*

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**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.*

Delays in issuance of subcontracts along with unanticipated and unapproved changes made by PAVIR to the TRIA subaward delayed hiring of personnel and initiation of the Stanford and TRIA clinical performance sites. Following approval of administrative transfer of the grant from PAVIR to Stanford, personnel have been hired and both clinical performance sites have been initiated.

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**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.*

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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

NA

Significant changes in use of biohazards and/or select agents

NA

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:

Nothing to report
**Stanford Primary Site:**

| Name: Constance R. Chu, MD | Project Role: Principal Investigator (Stanford) |
| Nearest person month worked: 3 | Contribution to project: Dr. Chu has overseen all study activities and expended substantial time on unanticipated subaward issues*. |

| Name: Mark Genovese, MD | Project Role: Study Co-PI (Stanford) |
| Nearest person month worked: 1 | Contribution to project: Dr. Genovese advised on Independent Study Monitor activities and assisted with the investigational pharmacy, FDA review, and with protocol refinement. |

| Name: Jennifer Erhart-Hledik, PhD | Project Role: Clinical Research Associate (Stanford) |
| Nearest person month worked: 1 | Contribution to project: Dr. Erhart-Hledik assisted with preparation of documents for local IRB approval and assisted with preparation of HRPO documentation. |

| Name: Ashley Williams, MS | Project Role: MRI Research Associate (Stanford) |
| Nearest person month worked: 2 | Contribution to project: Ashley coordinated purchase of MRI coil and installation of study MRI sequences for the TRIA site, assisted with establishment of MRI agreement between GE and TRIA site, optimized MRI DESS and Cones sequences for both study sites, attended the investigator meeting, assisted with testing and refinement of the MRI protocol. |

| Name: Karlos Zepeda, BS | Project Role: Clinical Research Coordinator Assistant |
| Nearest person month worked: 1 | Contribution to project: Karlos assisted with preparation of clinical recruitment materials and communication of study tasks and milestones with anticipated clinical recruitment sites. |

| Name: Michelle Backer, MS | Project Role: Collaborating Clinical Coordinator |
| Nearest person month worked: 1 | Contribution to project: Michelle advised and worked with Karlos on site initiation activities. |

| Name: Henry Truong, Pharm D | Project Role: Study Pharmacist |
| Nearest person month worked: 1 | Contribution to project: Dr. Truong assisted with obtaining the FDA exemption and obtained a Minnesota license to permit dispensing trial medications to the Minnesota site. |

| Name: Christine Le Hoang, MS | Project Role: Clinical Research Coordinator |
| Nearest person month worked: 3 | Contribution to project: Christine assisted with preparation of clinical recruitment materials, oversaw RedCap build, substantially developed the study operations protocol, |
**Stanford Primary Site continued:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Project Role</th>
<th>Nearest person month worked</th>
<th>Contribution to project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brittney Deadwiler, BS</td>
<td>Clinical Research Coordinator Associate</td>
<td>1</td>
<td>Britney assisted with preparation of clinical recruitment materials and systems, worked with Christine to finalize the study operation protocol, has efforted collaboration with Stanford athletic departments to facilitate subject recruitment.</td>
</tr>
</tbody>
</table>

**TRIA Minnesota Site:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Project Role</th>
<th>Nearest person month worked</th>
<th>Contribution to project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brad Nelson, MD</td>
<td>Study Co-PI (TRIA, Minnesota)</td>
<td>1</td>
<td>Dr. Nelson oversaw the Minnesota site activities.</td>
</tr>
<tr>
<td>Kelsey Schnackenberg</td>
<td>TRIA site Clinical Coordinator</td>
<td>3</td>
<td>Kelsey prepared and revised all documents for TRIA site approval and assisted with testing of the MRI protocols.</td>
</tr>
<tr>
<td>Megan Reams, MS</td>
<td>Research Manager (TRIA/Minnesota Site)</td>
<td>1</td>
<td>Megan assisted with study initiation and unanticipated continuing issues surrounding the TRIA subcontract.*</td>
</tr>
</tbody>
</table>
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.”

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.

PAVIR – Palo Alto Veterans Institute for Research
3801 Miranda Ave
Palo Alto, CA 94303-0038
Grant Administration

Stanford University School of Medicine, Department of Orthopedic Surgery
Stanford CA, 94035
Coordinating and Primary Clinical Performance Site

University of Minnesota, TRIA Orthopaedic Center
8100 Northland Drive, Bloomington, MN 55431
Clinical Performance Site

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.
### Project 3

<table>
<thead>
<tr>
<th>Award Number:</th>
<th>W81XWH1810590</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Number:</td>
<td>PR176147</td>
</tr>
<tr>
<td>Project Title:</td>
<td>Project 3 of Novel Strategies to Combat Post-Traumatic Osteoarthritis: Cellular Rejuvenation to Combat Post-traumatic OA</td>
</tr>
<tr>
<td>Principal Investigator Name:</td>
<td>Nidhi Bhutani, PhD/Co-PI Constance R. Chu, MD</td>
</tr>
</tbody>
</table>
| Principal Investigator Organization and Address: | Stanford University  
Department of Orthopedic Surgery  
300, Pasteur Drive  
Edwards Bldg R164  
Stanford, CA 94305-5341 |
| Principal Investigator Phone and Email: | nbhutani@stanford.edu |
| Report Date: | 08/28/2019 |
| Report Period: | 06/01/2019 – 08/31/2019 |

Email the report and any other attachments to the Grants Officer’s Representative (GOR) and Grants Specialist at the email addresses specified in the award document. Name the file with the award number, followed by “QtrlyTechProgReport Month Year.”

If you have questions, contact the GOR.
6. **ACCOMPLISHMENTS:** THE PI IS REMINDED THAT THE RECIPIENT ORGANIZATION IS REQUIRED TO OBTAIN PRIOR WRITTEN APPROVAL FROM THE AWARDING AGENCY GRANTS OFFICER WHENEVER THERE ARE SIGNIFICANT CHANGES IN THE PROJECT OR ITS DIRECTION.

**What were the major goals of the project?**

1. Major task 1: Establishing iPSC lines from donors undergoing ACL reconstruction (1-6 months)
2. Subtask 2: Procurement of donor cells from patients undergoing ACL reconstruction.

**What was accomplished under these goals?**

For **this quarterly reporting period only 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.

We obtained local Stem Cell Research Oversight (SCRO) approval for our iPSC studies. We obtained local IACUC approval for the athymic rat studies and ACURO approval for the animal studies. We have purchased and tested running wheels in preparation for initiating animal studies. We have initiated protocols for generating iPSC from monocytes obtained blood purchased from the blood bank in preparation for establishment of iPSC from ACL injured donors (Subtask 1) and their maintenance and expansion.

**Describe the Regulatory Protocol and Activity Status (if applicable).**

Describe the Protocol and Activity Status for sections a-c, as applicable, using the format described for each section. If there is nothing significant to report during this reporting period, state “Nothing to Report.”

**b) Human Use Regulatory Protocols**

**TOTAL PROTOCOLS:** None

**c) Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training**

**TOTAL ACTIVITIES:** No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).

**c) Animal Use Regulatory Protocols**

**TOTAL PROTOCOL(S): One**

*State the total number of animal use protocols required to complete this project (e.g., 2 animal use research protocols will be required to complete the Statement of Work.). If not applicable, write “No animal use research will be performed to complete the Statement of Work.”

**PROTOCOL ( 1 of 1 total):**

Protocol [ACURO Assigned Number]: pending
Title: Novel Strategies to Combat Post-Traumatic Osteoarthritis (PTOA): Cellular Rejuvenation to Combat Post-traumatic OA
Target required for statistical significance: 180 athymic rats
Target approved for statistical significance: 180 athymic rats
What do you plan to do during the next reporting period to accomplish the goals and objectives?

1. Initiate *in vitro* studies under Major Task 1.
2. Make any requested revisions to complete ACURO approval.
3. Initiate animal studies.

7. PRODUCTS: LIST ANY PRODUCTS RESULTING FROM THE PROJECT DURING THE REPORTING PERIOD. IF THERE ARE NO PRODUCTS TO REPORT FOR THE CURRENT QUARTER, STATE "NOTHING TO REPORT."

Nothing to report.

8. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

| Name: Nidhi Bhutani, PhD (Stanford) | Project Role: Principal Investigator |
| Researcher Identifier (e.g. ORCID ID): | Nearest person month worked: 1 |
| Contribution to Project: | Dr. Bhutani supervised the protocols and maintenance/expansion of donor cells. |

| Name: Constance Chu, MD (VA Palo Alto) | Project Role: Co-Principal Investigator |
| Researcher Identifier (e.g. ORCID ID): | Nearest person month worked: 1 |
| Contribution to Project: | Dr. Chu supervised completion of IACUC. |

| Name: Erika Leonardi, MD | Project Role: Chu Lab Post-doctoral Fellow (Stanford) |
| Researcher Identifier (e.g. ORCID ID): 1234567 | Nearest person month worked: 1 |
| Contribution to Project: | Dr. Leonardi assisted with completion of the IACUC. |

| Name: Michaela Bruschi, PhD | Project Role: Bhutani Lab Post-doctoral Fellow (Stanford) |
| Researcher Identifier (e.g. ORCID ID): | Nearest person month worked: 3 |
| Contribution to Project: | Dr. Bruschi assisted with maintenance/expansion of donor cells. |
9. CHANGES/PROBLEMS:

   c. Actual Problems or delays and actions to resolve them

| Delay in initiation of Stanford subcontract. Currently awaiting completion of grant transfer to Stanford. |

   d. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

| Project initiation was delayed as it took more time than anticipated to get the subcontract in place. |

10. SPECIAL REPORTING REQUIREMENTS:

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

    N/A
AWARD NUMBER:  W81XWH1810590

TITLE:  Project 4 of Novel Strategies to Combat Post-Traumatic Osteoarthritis: Gait Retraining to Reduce Inflammation, Joint Loading and PTOA Risk

PRINCIPAL INVESTIGATOR:  Constance R. Chu, MD

CONTRACTING ORGANIZATION:

REPORT DATE:

TYPE OF REPORT:  Annual

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

DISTRIBUTION STATEMENT:  Choose Distribution Statement A or B.  (Reference https://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting for additional information.)

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
4. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Following anterior cruciate ligament reconstruction (ACLR), a change in the loading environment at the knee has been suggested as a mechanism for accelerated osteoarthritis development. This study will use a prospective pre-post design to assess the effects of an active-feedback load-modifying gait retraining intervention in patients 2 years after ACLR. The study objective is to determine the magnitude and duration of changes to the knee adduction moment (KAM) following a novel active feedback gait retraining program, and to assess correlations between KAM changes and changes to the serum inflammatory response and cartilage matrix structure in ACLR patients. The gait retraining intervention is based on changing foot position through active feedback to shift pressure from the lateral to medial portion of the foot using pressure sensors in the shoe. Participants will complete 8 weekly laboratory retraining sessions and will be assessed over 6 months post-training.

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

Anterior cruciate ligament reconstruction, gait retraining, osteoarthritis, active feedback, gait analysis, knee adduction moment, magnetic resonance imaging, biomarkers

6. 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: Prepare for prospective “pre-post” study
- Subtask 1: Submit documents for local IRB review (target completion within months 1-3)
  - IRB approval received (completed in May 2018)
- Subtask 2: Submit IRB approval and necessary documents for HRPO review (target completion within months 4-6)
  - HRPO approval received (completed in October 2018)

Major Task 2: Participant Recruitment, Baseline Assessment, Gait Retraining Program, and Gait Analysis Follow-up Assessments
- Subtask 1: Recruit subjects meeting inclusion/exclusion criteria and perform baseline gait analysis (target completion within months 7-36)
  - 10% complete
- Subtask 2: Complete laboratory gait retraining sessions for enrolled participants (target completion within months)
  - 5% complete

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.

In the first year of this study, efforts focused on start-up activities, including preparation of all study materials and preparation for study initiation, as well as initiation of subject recruitment and testing. IRB approval, Veterans Affairs Research and Development Information System (RDIS) approval, and HRPO approval were obtained for the proposed protocol. Study investigators met regularly to discuss protocol details and planned study activities. Purchases of required study materials were completed in preparation for study start-up.

Human subject recruitment efforts are underway. Potential subjects have been identified via advertisements and chart review per study approvals, and as of the time of this report more than 100 recruitment letters inviting potential subjects to learn more about the study have been mailed. Interested individuals are in the process of screening for inclusion/exclusion criteria. Five individuals have been consented into the study, and two are currently completing the gait retraining study visits, with additional baseline study visits scheduled.
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 plan to continue our recruitment efforts, through both recruitment letters and study flyers. We will continue screening and enrolling study participants and begin baseline study assessments. Enrolled participants will begin and complete the gait retraining program, and will complete post-training follow-up assessments.

5. 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).

Nothing to Report.

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.**

---

**10. 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.

It was determined that Dr. Andriacchi’s VA status precluded him from serving as PI of a VA based project. As previously reported, the PI was changed from Thomas Andriacchi, PhD to Constance Chu, MD.

**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.

Joint Personnel Agreements needed to compensate Stanford Employees to work on this project and requested by the PI were not performed by PAVIR resulting in delay of project initiation.
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**

No changes.

**Significant changes in use or care of vertebrate animals**

Not applicable.

**Significant changes in use of biohazards and/or select agents**

No changes.

11. **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.

- **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);
  - new business creation; and
  - other.

Nothing to Report.
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”.

<table>
<thead>
<tr>
<th>Name:</th>
<th>Constance R. Chu, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role:</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Researcher Identifier (ORCID ID):</td>
<td></td>
</tr>
<tr>
<td>Nearest person month worked:</td>
<td>1</td>
</tr>
<tr>
<td>Contribution to project:</td>
<td>Dr. Chu has overseen study planning meetings and start-up activities.</td>
</tr>
<tr>
<td>Funding Support:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name:</th>
<th>Jennifer Erhart-Hledik, PhD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role:</td>
<td>Study Co-I</td>
</tr>
<tr>
<td>Researcher Identifier (ORCID ID):</td>
<td></td>
</tr>
<tr>
<td>Nearest person month worked:</td>
<td>1</td>
</tr>
<tr>
<td>Contribution to project:</td>
<td>Dr. Erhart-Hledik led preparation of study protocol planning and activities. She also worked on data collection.</td>
</tr>
<tr>
<td>Funding Support:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name:</th>
<th>Jessica Asay, MS (Stanford)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role:</td>
<td>Gait Mechanics Engineer</td>
</tr>
<tr>
<td>Researcher Identifier (ORCID ID):</td>
<td></td>
</tr>
<tr>
<td>Nearest person month worked:</td>
<td>1</td>
</tr>
<tr>
<td>Contribution to project:</td>
<td>Ms. Asay worked on preparation and testing of the gait retraining device along with preparation of study protocol and activities and data collection.</td>
</tr>
<tr>
<td>Funding Support:</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Name:</th>
<th>Karlos Zepeda, BS (Stanford)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role:</td>
<td>Clinical Coordinator</td>
</tr>
<tr>
<td>Researcher Identifier (ORCID ID):</td>
<td></td>
</tr>
<tr>
<td>Nearest person month worked:</td>
<td>1</td>
</tr>
<tr>
<td>Contribution to project:</td>
<td>Mr. Zepeda assisted with activities related to human subject recruitment.</td>
</tr>
<tr>
<td>Funding Support:</td>
<td></td>
</tr>
</tbody>
</table>
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.

13. 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.amedda.army.mil for each unique award.

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

14. 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.
Project 5

AWARD NUMBER:  W81XWH1810590

TITLE:  Localized Gene Therapy for Prolonged Anti-Inflammatory Treatment to Prevent or Delay PTOA in an Equine Model.

PRINCIPAL INVESTIGATOR:  Laurie Goodrich, DVM-PhD

CONTRACTING ORGANIZATION:  Colorado State University

REPORT DATE:  08/28/2019

TYPE OF REPORT:  Annual and Final Technical Report

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

DISTRIBUTION STATEMENT:  Choose Distribution Statement A or B.  (Reference
for additional information.)

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Post traumatic osteoarthritis (PTOA) has been shown to be the primary source of disability in warriors. To date there are no effective disease-modifying therapies and PTOA is still primarily diagnosed with radiographs, frequently after irreversible tissue damage has occurred. A potentially promising therapy involving the blockage of the IL-1β receptor with the administration of an IL-1ra gene therapeutic treatment may result in decreased joint catabolism. Short term clinical trials have indicated that the gene delivery of IL-1ra to affected joints have resulted in significant improvements in both clinical and histological outcomes. The achievement of the long-term production of these gene therapies may have significant and extended symptom and disease modifying benefits. Moreover, the identification of reliable biomarkers that accurately represent the stage and progression of PTOA, as well as the extent of response to treatment, are of crucial importance.

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

Gene therapy, post-traumatic osteoarthritis (PTOA), IL-1ra, biomarkers

8. 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.

1. To develop a safe and effective scAAV-based gene therapeutic approach to treat PTOA in the equine model.
2. To validate biomarkers in a time-sensitive manner as it relates to exercise in the equine model to reflect PTOA disease status and response to therapy.

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.

We have successfully obtained ACURO approval for this grant and are currently working on the generation of the scAAVIL-1ra gene therapeutic vectors for injection into OA induced carpi.

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.”

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

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

We plan to begin the study in horses.

6. 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).

Nothing to report

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

15. 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.

- 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.

- 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.

- 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
  NA

  Significant changes in use or care of vertebrate animals
  Nothing to report

  Significant changes in use of biohazards and/or select agents
  NA
16. 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).
  
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  **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).
  
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  **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.
  
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- **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.
  
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- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.
  
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- **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.
  
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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

17. 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: Jennifer Phillips
Project Role: Research Associate
Nearest person month worked: 1
Contribution to project: Ms. Phillips has performed the production and analysis of the plasmids needed to create the gene therapeutic agents.
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 |

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