

AWARD NUMBER: W81XWH-16-2-0036

TITLE: Mesenchymal Stem Cells for the Prevention of Acute Respiratory Distress Syndrome after Pulmonary Contusion and Hemorrhagic Shock

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14. ABSTRACT Patients who initially survive from traumatic thoracic injury are at risk for Acute Respiratory Distress Syndrome (ARDS). The only proven treatments available once ARDS has developed are low tidal volume ventilation (ARDSnet) and proning, but there is no existing treatment strategy to prevent the onset of ARDS following traumatic injury. As a potential solution, recent evidence suggest that the therapeutic administration of mesenchymal stem cells (MSCs) can prevent ARDS secondary to medical causes, but this has not been investigated in the trauma setting. Therefore, the purpose of this project is to conduct a series of in vitro and in vivo studies to determine if the therapeutic administration of MSCs prevents the development of ARDS following pulmonary contusion and hemorrhagic shock. During Year 1, we obtained both IACUC and ACURO approval, and have completed our model development phase for the swine model. To improve the well-being of the animals and maintain consistency in the model, we redesigned the protocol to keep the swine sedated for 48 hours using a combined inhaled and IV anesthetic regimen. In addition, we successfully harvested MSCs from swine bone marrow and expanded the cells on the Quantum with >80% viability. Future Quantum runs are scheduled to provide MSCs for the randomized study. Our plans for Year 2 include starting the randomized in vivo swine study, continue MSC cell expansion, and start the in vitro analysis of plasma, tissue and BAL samples from the study swine.					
15. SUBJECT TERMS Pulmonary contusion, animal model, mesenchymal stem cells, ARDS					
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Patients who initially survive from traumatic thoracic injury are at risk for Acute Respiratory Distress Syndrome (ARDS). The only proven treatments available once ARDS has developed are low tidal volume ventilation (ARDSnet) and proning, but there is no existing treatment strategy to *prevent the onset* of ARDS following traumatic injury. As a potential solution, recent evidence suggest that the therapeutic administration of mesenchymal stem cells (MSCs) can prevent ARDS secondary to medical causes, but this has not been investigated in the trauma setting. Therefore, the purpose of this project is to conduct a series of *in vitro* and *in vivo* studies to determine if the therapeutic administration of MSCs prevents the development of ARDS following pulmonary contusion and hemorrhagic shock.

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

Swine, shock, pulmonary contusion, mesenchymal stem cells, acute respiratory distress syndrome, liver injury, bone marrow, therapeutic potential of stem cells

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.

The major tasks listed in the SOW include:

- 1) Obtain regulatory approval and test model
- 2) Begin randomized study
- 3) Large scale expansion of swine MSCs
- 4) Testing of BAL and Blood Samples from swine for effects on vascular permeability *in vitro*
- 5) Histopathological analysis of swine lung tissue for vascular markers and inflammation
- 6) Testing of blood samples from swine for effects on vascular permeability using *in vivo* Miles Assay
- 7) Proteomics studies of lung tissue from swine and analysis of inflammatory cytokines and growth factors
- 8) Submit abstracts publications and final report to Army.

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 activities and specific objectives accomplished include:

1) Obtain regulatory approval and test model (Schreiber lab)

During Year 1, we have obtained approval from both OHSU IACUC and ACURO to develop our swine model of pulmonary contusion and hemorrhagic shock. We have conducted a series of experiments to develop this model, starting with the initial model described in the grant. However, our initial model development experiments showed that extubated the animals was not logistically or physically feasible. To improve the welfare of the animal and consistency in the model, we revised our model (with IACUC and ACURO approval) to keep the animals sedated for a 48 hour period using combined isoflurane and IV ketamine sedation. Using this new model, we have shown that pulmonary contusion (bolt gun) and hemorrhagic shock (Grade V liver injury) induced a progressive decline in PaO₂: FiO₂ over 48 hours (Figure 1A) accompanied by histological evidence of ARDS in the contralateral lung (Figure 1B).

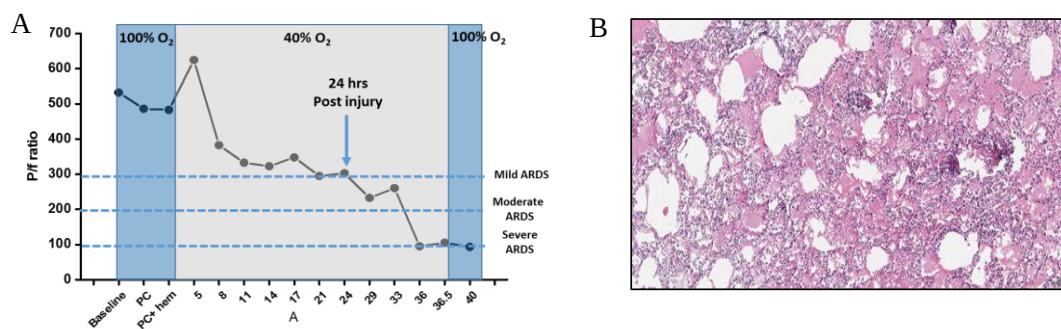


Figure 1. A. P/F ratio over time in injured swine; B. Histologic evidence of ARDS in uninjured contralateral lung.

2) Development and growing of swine MSCs (Pati lab)

To date the Quantum device has been run 16 times on the Swine MSC project.

The main goal of the past years efforts were to optimize the production, viability, cryopreservation, shipping, thawing, and recovery process for the swine MSC doses that are being shipped to OHSU for testing in the swine model of ARDS induced by pulmonary contusion and hemorrhagic shock.

The production of adequate quantities of MSCs is on the Quantum Bioreactor and this has required a number of developmental runs to optimize all aspects of the process. Below are listed the expansions procedures and results of Quantum runs.

Characterization of MSC by Flow Cytometry:

The minimum criteria for qualification of cells as MSCs can be obtained by flow cytometry. Similar to the criteria set down by the International Society for Cellular Therapy (ISCT) for human MSCs we adopted a similar approach for Swine MSCs but with some slight variation due to the availability of antibodies. Under ISCT criteria, human MSCs should be positive for CD105, CD90, and CD73. MSCs are also known to express numerous cell surface markers such as CD44. Human MSCs should also be negative for contaminant markers CD45, CD34 and HLA-DR. The panel assembled for the identification of swine MSCs includes the positive markers CD105, CD90, CD73 and CD44. Negative markers are CD45, CD31 and SLA-DR. Development of the panel has now been completed. Based upon these markers, P3 cells generated from Pig8 met criteria as Swine MSCs.

(1) Cell Expansion.

The typical hands-on time for growing swine MSCs on the Quantum is 11 days. The timing of harvest is dependent on the plateau/slow down of lactate production which indicates decreased cell division, hence the time of optimal harvest was determined. See figure 1 for sample of glucose and lactate readings for swine MSC expansion on the Quantum. The glucose lactates are feed back measures from this device since cells cannot be directly visualized.

- **Quantum Run #3, May15th-> May24th (Conservative feed- .1-1.2 mls/minute over 7 day ramp up)**
Goal: The goal of this run was to test a conservative feed rate on the production of the cells. This conservative feed rate may allow us to optimize utilization of the MSC media and reagents required for cell growth.
10 million swine MSCs were loaded onto the TerumoBCT Quantum Bioreactor platform. Cells were sourced from the 2nd bone-marrow delivered (Pig2 from the OHSU group) that arrived at BSRI in Quarter 1 and were grown-up and frozen at the Passage1 stage. Output from the Quantum, following a successful 7 day run was 360 million cells. Based upon notion that average pig is 45 kg and the infusion was to be at 5×10^6 cells/kg cells were divided into bags (225 million and 125 million). Sterile cryobags (CryoMACS Freezing Bag 50) were obtained from MiltenyBiotec on the recommendation of Dr David McKenna, Director of Cell Processing at the University of Minnesota. Cells were frozen down using a Controlled Rate Freezing (CRF) protocol that was utilized by Blood Systems -CTS for human MSCs in our human MSC production program.
- **Quantum Run #4, May 25th-> June 2nd (Aggressive feed-.1-2 mls/minute ramp up over 7 days)**
Goal: The run was designed to assess whether a higher feeding rate strategy would alter output. **Results:** 10 million swine MSCs were loaded (The same source (Pig2) as with Quantum Run #3), output was also 360 million cells. Subsequently all future runs will be conducted using the conservative feed protocol. Cells released from the bioreactor were divided into bags (225 million and 125 million).
To generate more cells for Quantum Runs additional swine bone-marrow was shipped from OHSU to BSRI on May 30th. Cells were grown up in tissue-culture flasks over a 2 week period to generate a P1 population. These indicate that a higher feed rate does not increase cell production so we are planning to stay with a conservative feed rate for all dose production,
- **Quantum run #5 and #6 June 19th -> June 30th**
Goal: To produce cell doses for development swine runs at OHSU
With cells from Pig7, concomitant Quantum runs on both devices were started on June 19th. Although both machines ran with conservative feed protocols the number of cells loaded was increased from 10 to 15 million loading dose to see if we could increase output. Both machines ran without issue until the point of harvest. At which point one machine gave a lower output volume than the other machine (200 ml vs. 350 ml). Output from the harvest was recorded at 305 and 368 million cells respectively, indicating that there may be an issue with one of the devices. TerumoBCT were notified of the issue and we are looking into this for our next runs.

- **Masterbank of cells**

To ensure the maximal control over variability and the minimum requirement for pigs as donors of bone marrow therapeutic doses shall be used from the P3 generation. In brief cells grown from bone marrow in tissue culture are P1. Cells grown from the bone-marrow P1 cultures on the Quantum are P2, which form the master bank of cells. P3 cells are cells that have undergone 2 expansions on the Quantum and are cells to be used as therapeutics. P1 generation cells were grown and are in storage for PIG8, PIG9 and PIG10. To date a master bank of cells has been produced from PIG8.

- **Quantum run #9 (Aug 3rd - Aug 11th)**

Goal: Generate a Master bank of cells (P2 generation) from PIG8 for future P2->P3 runs.

Machine ran without issue and generated 340 million cells for the master bank. Cells were frozen down in 1ml cryovials for P3 runs.

- **Quantum run #10 (Aug 14th - Aug 23rd)**

Goal: First P3 Expansion using PIG8 master bank

Machine ran without issue and generated 290 million cells

- **Quantum run #11 (Aug 23rd - Sept 1st)**

Goal: Second P3 Expansion using PIG8 masterbank

A technical issue developed with the disposable set resulting in a truncated volume and cellular output. The result only generated 180 million cells resulting in 3 vials of 50×10^6 cells

- **Machine replacement**

Further problems with machine 107 rendered it inactive. The Machine was finally replaced by TerumoBCT on the 28th of August.

- **Quantum run #12 and #13 (Sep 12th - Sept 20th)**

Goal: Third and fourth expansions using PIG8 master bank.

First concomitant run since June due to machine issue. Both Machines ran without issue and generated 340 and 300 million cells respectively.

- **Quantum run #14 (Sept 24th – October 3rd)**

Goal: fifth expansion using PIG8 master bank.

Machine ran without issue and generated 325 million cells

- **Quantum run #15 (Oct 1st – October 10th)**

Goal: sixth expansion using PIG8 master bank.

Machine ran without issue and generated 275 million cells

Current Inventory of doses:-

31 vials at $50 \times 10^6 = 7.75$ doses. Goal is to have the doses needed for the first block of swine by Nov. 20th, 2017. The cells block of MSCs will be shipped to OHSU in Liquid Nitrogen Shippers.

(2) Viability.

The initial exercise in shipping cells in cryobags from BSRI to OHSU has highlighted the need for procedural refinement. Low cell recovery/enumeration and compromised viability was observed at about 60%. Ongoing internal experiments at BSRI have identified that the cryobags have a higher retention in the bag (cells remaining in the bag) than cryovials which has warranted a reevaluation of their use.

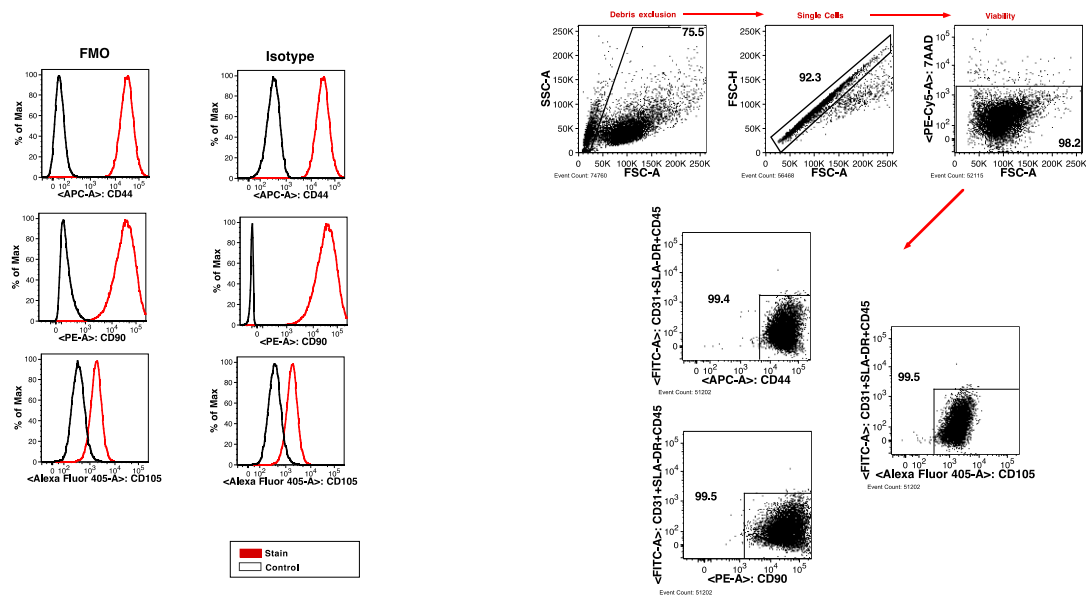
The method of Cryopreservation (via controlled rate freezing protocol) was also deemed to be suspect for the preservation of viability. Internal experiments at BSRI indicated that Cryovials and controlled rate freezing via the Biocision system provided the best route forward.

In addition, shipping cells on dry ice as opposed to liquid nitrogen shippers may result in reduced viability. We are planning to ship all doses in LN2 shippers and all cells in cryovials (through contracting via Cryoport <http://www.cryoport.com/>) so as to address decreased viability and recovery.

Since our initial observations we have reevaluated the system to include several new aspects. This has included the acquisition of 5ml Cryovials and controlled rate cool cell freezing units. The viability post-thaw is improved to greater than 80%.

(3) Cell marker expression.

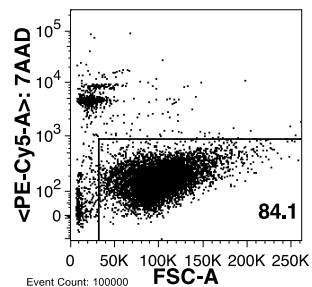
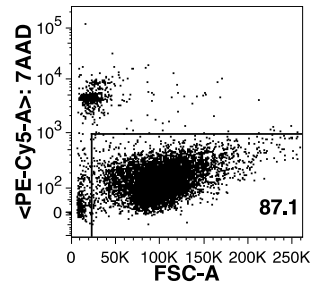
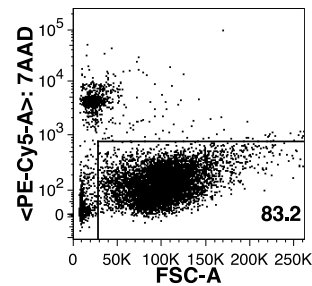
Analogous to human MSCs where ISCT criterion for what defines a MSC is applicable for the P1 generation onwards (but not P0 cells) we have generated a flow cytometry testing panel for swine MSC. The panel will include both positive and negative markers to verify identity. The markers that will be tested are CD105, CD90 and CD44. Negative markers are CD45, CD31, and SLA-DR (Swine HLA-DR). and CD73



Viability

Avg= 84.8%

Single stain: 7AAD
Single viability gate



In the 3rd panel, Exploration of cell integrity using 7-AAD has revealed a high viability profile (>80%) of cells resuscitated from Cryovials.

The main goal of our future plans is to generate adequate and high quality doses for OHSU swine studies. We are optimizing cell number production, cryopreservation, shipping, thawing and infusion protocols.

We have established a plan for runs for the next block of cells

Runs 17,18	Wednesday 18 th October to Friday 27 th * October	Double Run
Runs 18,19	Monday 30 th October to Wednesday 8 th November	Double Run
Runs 20,21	Wednesday 8 th November to Friday 17 th November	Double Run
Runs 22,23	Monday 20 th November to Wednesday 29 th November	Double Run
Runs 24,25	Wednesday 29 th November to Friday 8 th December	Double Run
Runs 26,27	Monday 11 th December to Wednesday 20 th December	Double Run
Runs 28,29	Wednesday 20 th December to Friday 29 th December	Double Run

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.

For Year 2, our goals are to start the following tasks:

- 1) Begin randomized study (Schreiber)
- 2) Continue large scale expansion of swine MSCs (Pati)
- 3) Test BAL and Blood Samples from swine for effects on vascular permeability *in vitro* (Pati)
- 4) Histopathological analysis of swine lung tissue for vascular markers and inflammation (Pati)
- 5) Testing of blood samples from swine for effects on vascular permeability using *in vivo* Miles Assay (Pati)

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.*

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.

As described in Section 3, we had to change the model to complete sedation over 48 hours to improve consistency in the model and the well-being of the animals. These changes have been approved by both the OHSU IACUC and ACURO.

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.

Due to the change in the model, we are slightly delayed in starting our randomized study. However, to compensate from this delay we will double the number of experiments conducted per week.

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

Not applicable.

Significant changes in use or care of vertebrate animals

As described in Section 3, we had to change the model to complete sedation over 48 hours to improve consistency in the model and the well-being of the animals. These changes have been approved by both the OHSU IACUC and ACURO.

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).*

Smith SG, McCully BH, Bommmiasamy A, Murphy JM, Pati S, Goodman A and Schreiber MA. A Combat Relevant Model for the Creation of Acute Lung Injury in Swine. Submitted to <i>J Trauma</i> 10/14/17, currently under review.
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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).*

Nothing to report

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

Nothing to Report.

- **Website(s) or other Internet site(s)**

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

Nothing to Report.

- **Technologies or techniques**

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

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

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

Nothing to Report.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

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”.

OHSU:

Martin Schreiber, MD – no change

Belinda McCully, PhD – no change

James Murphy, MD – no change

Name: Andrew Goodman

Project Role: Coordinator

Research Identifier:

Nearest person month worked: 4

Contribution to project: Andrew performs various roles in administration, animal sedation, surgery, and sample processing.

Name: Sawyer Smith, MD

Project Role: Research Resident

Researcher Identifier:

Nearest person month worked: 4

Contribution to project: Dr. Smith is the lead resident on the project. He prepares and performs the swine surgery, monitors the experiment, organizes data and prepares data for presentation.

Name: Brandon Behrens, MD

Project Role: Research Resident

Researcher Identifier:

Nearest person month worked: 4

Contribution to project: Dr. Behrens assists Dr. Smith in preparing for and performing the swine surgery, and monitoring the experiment.

USCF

Shibani Pati MD, PhD – no change

Stuart Gibbs PhD – no change

Mars Stone, PhD – no change

Alpa Mahuvakar, PhD – no change

Daniel Potter, PhD – no change

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.*

Dr. Pati has moved her laboratory from BSRI to University of California San Francisco. Her role in the grant has not changed.

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.

Not applicable

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

Not applicable