AD_____

AWARD NUMBER: W81XWH-16-2-0036

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

PRINCIPAL INVESTIGATOR: Martin Schreiber, MD

CONTRACTING ORGANIZATION: Oregon Health & Science University
Portland, OR 97239

REPORT DATE: October 2018

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

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Annual

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6. AUTHOR(S)
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E-Mail:

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Oregon Health & Science University
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Blood Systems Research Institute
270 Masonic Avenue, San Francisco, CA 94188

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

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

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
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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 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) <u>Completed model development for in vivo swine model of pulmonary contusion & hemorrhagic shock.</u>

During Year 2, we modified our protocol to a non-survival model, by which the animal is under constant sedation for up to 72 hours to eliminate any pain or distress for the animal following pulmonary contusion, liver injury or both. Due to the length of time that it took to redevelop the model, we finished the initial model development phase at the end of October 2018.

Using our revised non-survival model, we started the randomized study on 2/6/18 and completed 10 experiments. All personnel involved in the surgical procedures were blinded to the treatment (vehicle vs MSCs). The only unblinded person was the individual who prepared the MSCs or vehicle for infusion. Within the 10 experimental animals, 4 animals died before the final 48-hour time point. These deaths were accompanied by hyperthermia and hyperkalemia, leading to cardiac arrest. The early occurrence of hyperkalemia and high mortality did not occur during the model development phase. Therefore, we placed the study on hold to determine the cause of the hyperkalemia and early death.

In speaking with an outside veterinarian, it is possible that these symptoms may be due to a variant of malignant hyperthermia (MH) that occurs in swine. To prevent the MH, we modified our IACUC and ACURO protocols to prophylactically treat the swine with Dantrolene at induction. After implementing this treatment regimen, the swine do not show the steady increase in temperature as they did in previous animals. However, it did not resolve the hyperkalemia or early mortality that we saw with previous experiments.

To address the continued hyperkalemia and high mortality, we developed a treatment regimen to mitigate the hyperkalemia and improve survival. Per our protocol, we implemented an aggressive care (AC) resuscitation by which initial intravenous fluids were given at a higher rate (7.5 ml/kg/hr, which is ~300ml/hr) compared to standard care (SC) maintenance fluids (90ml/hr). If an animal has a K+ > 5 mmol/L, it was be treated with insulin (10U), glucose (50g), and calcium (5mEq/kg) to lower K+ to <5

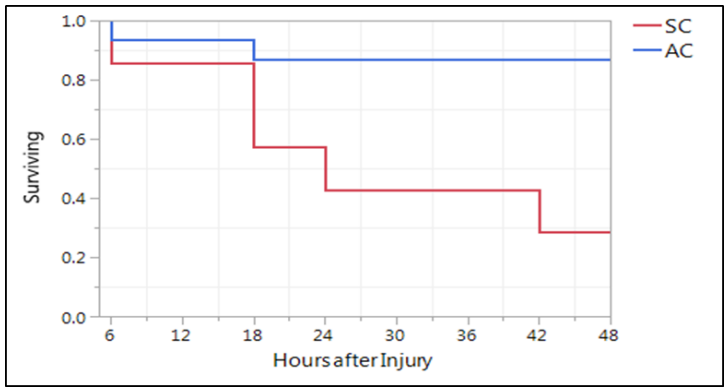


Figure 1. Compared to standard care (SC) resuscitation, implementing the aggressive resuscitation (AC) protocol with acute treatment for hyperkalemia improved survival in our model. P=0.008 SC vs AC.

mmol/L. Implementing the AC protocol lowered our mortality rate compared to animals under the SC protocol (Figure 1).

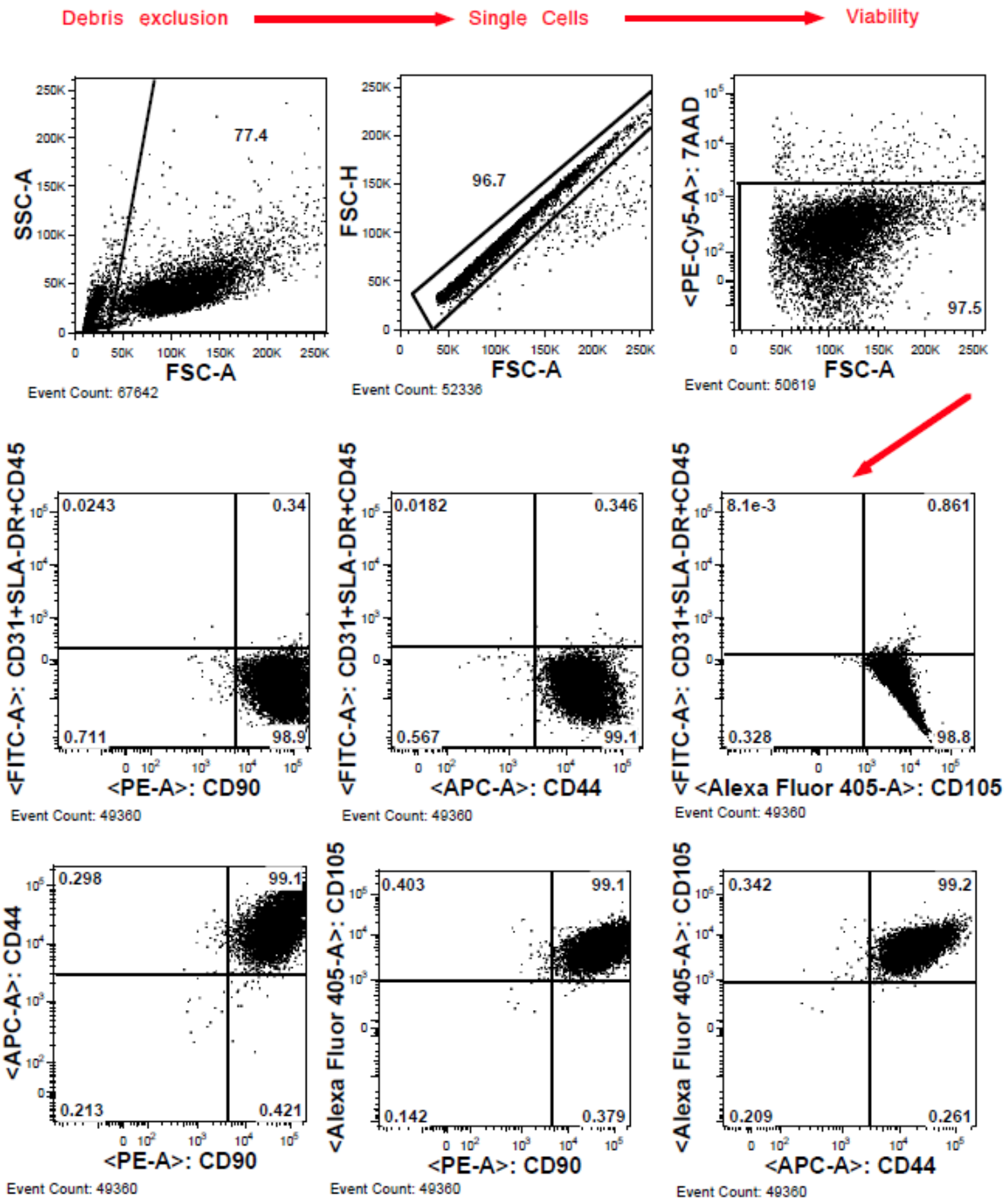
2) Continued development testing and growing of swine MSCs (Pati lab)

The main goal of the past year's effort was to continue the production of swine MSC doses. The MSC master bank production from donor swine and characterization of the MSCs are being used for the studies. As the doses are being produced, they are being shipped to OHSU for testing in the swine model of ARDS induced by pulmonary contusion and hemorrhagic shock. On January 10th, 80 vials of swine MSCs were shipped from BSRI to OHSU on a Cryoport LN2 shipper and stored in LN2 at OHSU.

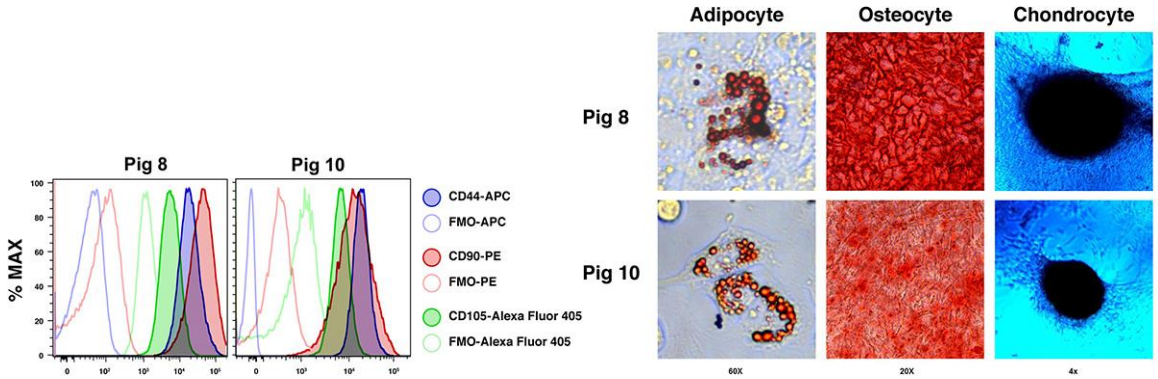
We expanded more swine MSC from donor pig 10 on Quantum. These cells have the best post-thaw viability, cell proliferation rate and functionality. We generated a total of 68 vials of 50 million cells per vial. One dose is 4 vials (200 million cells). So this generated 17 doses of cells. Each pig gets two doses, so there are enough cells for 8 pigs and one extra dose. All these cells were frozen in liquid nitrogen and shipped in liquid nitrogen to OHSU on 10-10-18.

Testing has also begun of the conditioned media from the swine MSCs in comparison to the human MSCs to gauge functional capability of the cells in measures of endothelial protection and inflammation by MLR reactions. Capacity of the MSCs to differentiate into all three lineages (osteocytes, chondrocytes and adipocytes) is also under way for both donor swine (Pig 8 and Pig 10). Below is the flow cytometric characterization of Pig 10 for markers of MSCs. The marker successfully indicate that cells are likely MSCs.

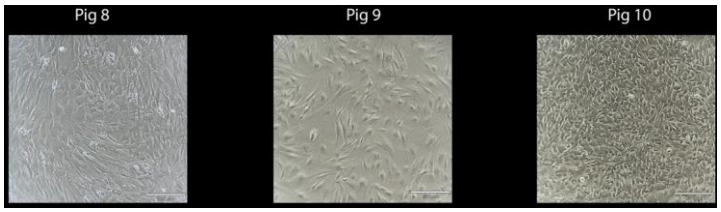
In the last quarter P3 cells were assayed for pigs 8 and 10 by flow cytometry for MSC markers. The viability of the cells was excellent, over 97% for cells from both pigs. In addition, each MSC marker was expressed on over 95% of the cells for both batches (data from pig 8 shown below).



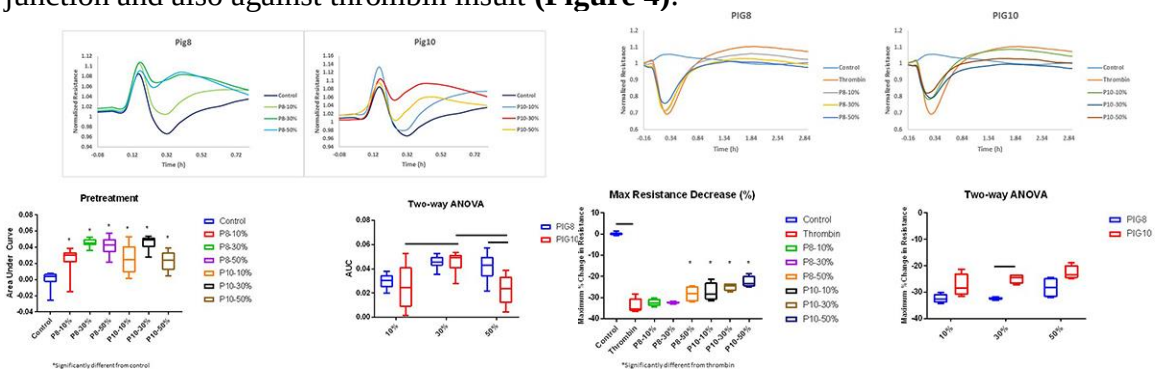
Flow cytometric characterization of cells from two different donors at passage 3 for markers of MSCs were successfully completed and indicate that cells express MSC antigens.



Capacity of these cells (donor swine Pig 8 and Pig 10) to differentiate into all three lineages (osteocytes, chondrocytes and adipocytes) has also been completed (**Figure 2**). Here we show bright field images of cells in culture form three different donors at passage 3 (**Figure 3**). Even though morphologically the cells look different between the donors, they express MSC markers to the same extent and have same differentiation pattern.



We have tested the conditioned media from the swine MSCs in measures of endothelial protection. Below is the plots showing that both conditioned media are protective for tight junction and also against thrombin insult **(Figure 4)**.



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.

This work was presented at the annual AABB meeting, CTTACC workshop by Dr. Shibani Pati The data regarding the treatment for hyperkalemia was presented by Dr. Sawyer Smith at the Region X American College of Surgeons Committee on Trauma Competition on December 1, 2018. The paper won the basic science paper competition and will be submitted for consideration to the National ACS COT competition.

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 3, our goals are to start the following tasks:

1) Begin randomized study in November 2018 (Schreiber)
2) Continue large scale expansion of swine MSCs (Pati)
3) Test Blood Samples from swine for effects on vascular permeability *in vitro* (Pati)
4) Histopathological analysis of swine lung tissue for vascular markers and inflammation (Schreiber)
5) Immunological analysis of swine tissue for markers of inflammation and vascular permeability (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 modified the model to prevent malignant hyperthermia, hyperkalemia, and early mortality. 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.

Nothing to report.

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. *J Trauma* 018 Jul;85(1S Suppl 2):S39-S43.

Alpa Trivedi, Byron Miyazawa, Stuart Gibb, Kristen Valanoski, Lindsay Vivona, Maximillian Lin, Daniel Potter, Mars Stone, Philip J. Norris, James Murphy, Sawyer Smith, Martin Schreiber, and Shibani Pati The Impact of MSC Donor Variability on Selection of the Optimal Donor for Cell Dose Production Cytotherapy (Under review).

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.*

This work was presented at the annual AABB meeting, CTTACC workshop by Dr. Shibani Pati
Mention here Sawyer's presentation for competition.

- **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

Name: Martin A. Schreiber, MD
Project Role: PI
Nearest person month worked: 0.9 calendar months
Contribution to Project: Dr. Schreiber has provided oversight and day-to-day management of the grant.

Name: Belinda H. McCully, PhD
Project Role: Co-investigator
Nearest person month worked: 0.9 calendar months
Contribution to Project: Dr. McCully has trained new personnel and managed the daily aspects of the experiments and model development.

Name: James M. Murphy, MD
Project Role: Research Associate/Veterinary Technician
Nearest person month worked: 3.0 calendar months
Contribution to Project: Dr. Murphy is responsible for the designing the anesthesia/sedation regimen, surgical preparation, and overall care of the animals during surgery and recovery.

Name: Sawyer Smith, MD
Project Role: Research Resident
Nearest person month worked: 3.0 calendar months
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: Andrew Goodman
Project Role: Coordinator
Nearest person month worked: 3.0 calendar months
Contribution to project: Andrew performs various roles in administration, animal sedation, surgery, and sample processing.

Name: James Russo
Project Role: Coordinator
Nearest person month worked: 3.0 calendar months
Contribution to project: James performs various roles in administration, animal sedation, surgery, and sample processing.

Name: Maria-Luisa Appleman
Project Role: Coordinator
Nearest person month worked: 3.0 calendar months
Contribution to project: Luisa performs various roles in administration, animal sedation, surgery, protocol management and sample processing.

Name: Brianne Madtson
Project Role: Coordinator
Nearest person month worked: 3.0 calendar months
Contribution to project: Brianne performs various roles in administration, protocol management, treatment preparation, ordering, and sample processing.

UCSF
Name: Shibani Pati MD PhD
Project Role- PI UCSF
Nearest person month worked: 0.45 calendar months
Contribution to project: Supervised design and execution of all work and studies. Review data and coordinates groups.

Name: Alpa Mahuvakar, PhD
Project Role: Scientist
Nearest person month worked: 1.35 calendar months
Contribution to project: Involved in planning and execution of studies, coordination with OHSU, running and coordination of in vivo mice experiments.

Name: Byron Miyazawa B Sc.
Project Role: Scientist
Nearest person month worked: 1.65 calendar months
Contribution to project: Running of Quantum, analysis of tissue and blood samples, running assays in vitro and on ex vivo tissue, cell analysis of swine MSCs.

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.*

None

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