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TITLE: Prothrombin Complex Concentrate for Prolonged Field Care of War Casualties

PRINCIPAL INVESTIGATOR: Martin Schreiber, MD

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Portland, OR 97239

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Oregon Health & Science University Portland, OR 97239

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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 prothrombin complex concentrate (Kcentra) acts similarly to plasma to prevent vascular leak and edema, 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 Kcentra prevents the development of ARDS following pulmonary contusion and hemorrhagic shock.

15. SUBJECT TERMS

None Listed

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			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 prothrombin complex concentrate (Kcentra) acts similarly to plasma to prevent vascular leak and edema, 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 Kcentra 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, endotheliopathy.

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?
   The major tasks listed in the SOW include:
   1) Obtain regulatory approval, run Rat HS model
   2) Run mouse model of hemorrhagic shock to test doses of Kcentra
   3) Tissue and Molecular Analysis of Rat Model of HS
   4) Run randomized study in swine model of lung injury and hemorrhagic shock
   5) Obtain regulatory approval and test swine model.
   6) Begin randomized study in swine
   7) Assess blood and tissue samples for inflammation
   8) Submit abstracts, publications, and final report to Army

   What was accomplished under these goals?
   Major activities and specific objectives accomplished include:

   Major Task #1: Obtain regulatory approval, Rat HS model (UCSF)
   UCSF acquired IACUC approval on 10/24/2017 and ACURO approval on 1/10/2018.

   Rat model of hemorrhagic shock 100% completed.

   Major Task #2: Model of HS, 24 hour survival (Changes planned for a switch from rats to mice) (UCSF) (20% complete)

We have received IACUC and ACURO approval to switch from rats to mice for the 24 hour model. Due to COVID-19 stay in place order, we were delayed in starting this study. We have begun to run the 24 hour model in mice and will analyze the effect of PCC on lung pathology, inflammation and inflammatory gene expression..

Major Task #3: Tissue and Molecular Analysis of Rat Model of HS (UCSF). 100% completion
We have completed the acute model of HS in rats and have published our work. Our work demonstrates critical variability in rodent models for testing of human products.

Potter, Daniel R. PhD; Trivedi, Alpa PhD; Lin, Maximillian BA; Miyazawa, Byron Y. BA; Vivona, Lindsay R. BA; McCully, Belinda PhD; Nair, Alison MD; Schreiber, Martin A. MD; Pati, Shibani MD, PhD The effects of human prothrombin complex concentrate on hemorrhagic shock-induced lung injury in rats: Implications for testing human blood products in rodents, Journal of Trauma and Acute Care Surgery: December 2020 - Volume 89 - Issue 6 - p 1068-1075 doi: 10.1097/TA.0000000000002890

Major Task #4: Obtain regulatory approval and test swine model (OHSU). 100% completion.
OHSU acquired their most recent IACUC approval on 8/31/2018 and ACURO approval on 10/2/2018.

The model development was completed in October 2018. The details of this model development are describe in the 2018 annual report.

Major Task #5: Run randomized study in swine model of lung injury and hemorrhagic shock (OHSU). 100% completion.
Utilizing our revised protocol developed in 2018, the randomized study is 100% complete as of February 2020. Physiologic data (hemodynamic variables, thrombelastography parameters, blood gases/chemistries) were collected during the protocol and recorded in a database. Plasma and tissue (lung, spleen, kidney, heart) samples were banked for future analysis. Following completion of the experimental work, analysis of the plasma and tissue samples was initiated. The lab at OHSU was closed due to the coronavirus during the spring of 2020, so assays were delayed but progress has been made in histology, PCR and luminex assays.

In the 2018 annual report, we reported that the use of an aggressive resuscitation regimen counteracts the development of hyperkalemia following pulmonary contusion and hemorrhagic shock. Dr. Sawyer Smith presented these findings at the 2019 North Pacific Surgical Association meeting. This paper won the Resident Prize for the Best Basic Science paper, and was published in May of 2020 by the American Journal of Surgery.

Dr. Alexandra Dixon presented her abstract on physiological study results, “FFP maintains normal coagulation while PCC induces a hypercoagulable state in a porcine model of pulmonary contusion and hemorrhagic shock”, to American College of Surgeons, Committee on Trauma,

Region X, winning the top prize for basic science. Her paper under the same title, will be published next year.

Major Task 6: Assess Blood and Tissue Samples for Inflammation. 20 % completion.
We will begin to analyze these samples in early 2020. The analysis process was initiated in February following the completion of the animal experiments. We have experienced some delays and limited lab access due to coronavirus restrictions, but anticipate increased analysis in 2021.

Major Task #7: Submit abstracts, publications, and final report to Army. 0% completion.
This task will be completed at the end of the study.

What opportunities for training and professional development has the project provided?
Nothing to Report.

How were the results disseminated to communities of interest?
In September of 2020, Dr. Schreiber presented results from the study to MRMC Grant Update Panel.

Additionally, as indicted above, Dr. Alexandra Dixon, presented results from this study and won the basic science competition for Region X, CoT.

What do you plan to do during the next reporting period to accomplish the goals?
Our goals for Year 5 include the following tasks:

1) Complete analysis of swine lung tissue and plasma samples for markers of inflammation and vascular damage (Schreiber)
2) UCSF –complete the 24h mouse model study that includes generation of the tissue and histological and molecular analysis
3) Submit abstracts for presentation at national meetings
4) Submit manuscripts for publication

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?
Nothing to Report

What was the impact on other disciplines?
Nothing to Report

What was the impact on technology transfer?
Nothing to Report

What was the impact on society beyond science and technology?
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
Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to Report.

Changes that had a significant impact on expenditures
Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report

Significant changes in use or care of human subjects
Nothing to Report.

Significant changes in use or care of vertebrate animals
Nothing to Report.

Significant changes in use of biohazards and/or select agents
Nothing to Report

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

- **Journal publications.**
  Potter, Daniel R. PhD; Trivedi, Alpa PhD; Lin, Maximillian BA; Miyazawa, Byron Y. BA; Vivona, Lindsay R. BA; McCully, Belinda PhD; Nair, Alison MD; Schreiber, Martin A. MD; Pati, Shibani MD, PhD The effects of human prothrombin complex concentrate on hemorrhagic shock-induced lung injury in rats: Implications for testing human blood products in rodents, Journal of Trauma and Acute Care Surgery: December 2020 - Volume 89 - Issue 6 - p 1068-1075doi: 10.1097/TA.0000000000002890

  Smith S, Behrens B, McCully B, Murphy J, Bommiasamy A, Goodman A, Dewey E, Pati S, Schreiber M. Aggressive Treatment of Acute Kidney Injury and Hyperkalemia Improves Survival in a Combat Relevant Trauma Model in Swine. Am J of Surgery, May 2020, 219 (5), 860-864.

- **Books or other non-periodical, one-time publications.**
  Nothing to Report.

- **Other publications, conference papers and presentations.**
  Nothing to Report.

- **Website(s) or other Internet site(s)**
  Nothing to Report

- **Technologies or techniques**
  Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Nothing to Report.

- **Other Products**
  Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

OHSU
Name: Martin A. Schreiber, MD
Project Role: PI
Nearest person month worked: 1.8 calendar months
Contribution to Project: Dr. Schreiber has provided oversight and day-to-day management of the grant.

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: Alix Dixon, MD
Project Role: Research Resident
Nearest person month worked: 3.0 calendar months
Contribution to project: Dr. Dixon is the lead resident on the project. She 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: 6.0 calendar months

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

Name: Maria Luisa Appleman, PhD
Project Role: Coordinator
Nearest person month worked: 6.0 calendar months
Contribution to project: Dr. Appleman performs various roles in administration, animal sedation, surgery, protocol management and sample processing.

Name: Brianne Madtson
Project Role: Coordinator
Nearest person month worked: 4.5 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: 1.8 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: 5.4 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: 6.6 calendar months
Contribution to project: In vitro assays and in vivo work.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report

What other organizations were involved as partners?
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