

AWARD NUMBER: W81XWH-19-2-0061

TITLE: Identification of Mechanisms Underlying the Effects of Plasma Inclusive Resuscitation in Major Thermal Injury on Hemostasis and Vascular Homeostasis

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CONTRACTING ORGANIZATION: MedStar Health Research Insititue

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1. INTRODUCTION:

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

The initial treatment of shock following thermal injury is swift infusion of isotonic crystalloids at a rate that is proportional to the percent total body surface area (TBSA) of cutaneous injury and the patient's pre-injury body weight. This often results in patients receiving in excess of 20 liters of fluid in the first 24 hours post-injury. Much of this massive volume then shifts to interstitial space causing edema-associated morbidities (pulmonary edema, burn depth progression, or compartment syndromes). Early resuscitation formulae included colloids that were introduced post-injury but for the most part these are of historic consideration as they were found to be inferior to the Brooke and Parkland methodologies. Recently, investigation is re-emerging on optimizing burn shock resuscitation. Areas of interest include a variety of strategies for reducing volume requirements (as would be needed in an austere environment—or where prolonged field care is required). Colloid is again being trialed in attempts to improve the response to vascular leakage, intravascular volume expansion and reduction of volume. Off-the-shelf colloid options include human serum albumin and fresh frozen plasma (FFP). Many prescribers of FFP report great response in regards to intravascular volume expansion with minimal side effects, though some reports exist of transfusion associated complications. Unfortunately, little is known about the impacts of these transfusion products on thermally-injured patients. Hence this proposal outlines a study that will elucidate the impact of a plasma-inclusive resuscitation (PIR) which will advance strategies for prolonged field care (i.e. freeze-dried plasma).

2. KEYWORDS:

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

Burn injury, thermal injury, burn resuscitation, fresh frozen plasma, inflammation, endotheliopathy, coagulopathy, resuscitation, systems biology, vascular homeostasis, transfusion reaction, extracellular vesicle

3. ACCOMPLISHMENTS:

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Major Task 1: Secure Regulatory Approval and Plan for Screening and Enrollment Coverage:

100%

Subtask 1: Clinical study/human subjects protocol preparation; data collection systems setup

100%

Subtask 2: Material and supply acquisition and on-call scheduling for screening; Staff

training for enrollment, sample acquisition, and data abstraction **100%**

Local IRB Approval and submission to HRPO: **100%**

Milestone Achieved: HRPO Approval

Major Task 2: Patient Enrollment and Sampling: 25%

Subtask 1: Enroll patients and obtain complete sample sets as described **60%**

Subtask 2: Obtain clinical data and enter into database in real time **20%**

Subtask 3: Transfer samples to collaborating sites for assay **20%**

Subtask 4: Establish multi-donor pool of healthy human plasma **0%**

Milestone(s) Achieved: samples obtained and transferred for assay, clinical data set being compiled

Specific Aim 1: To assess changes in the inflammatory state of burn patients undergoing a resuscitation protocol that includes plasma transfusion

Major Task 3: Measure inflammatory markers: 0%

Subtask 1: RNA isolation and whole genome microarray analysis (PAXgene blood)
0%

*Subtask 2 (Aim 1a. Understand the inflammatory potential of plasma products):
Inflammatory marker protein panel quantification including IL-1b, IL-6, IL-10, IL-12p70,
TNF- α , TNF- α R1/R2 and sIL-6 receptor (blood samples and FFP satellites/samples)*
0%

Milestone(s) Achieved (Aim 1b. Identify and characterize a further modulation of the host response by FFP administration in the setting of major thermal trauma): Inflammatory data obtained and integration with clinical and other data

Specific Aim 2: To assess changes in the vascular homeostasis and endothelial function of burn patients undergoing a resuscitation protocol that includes plasma transfusion

Major Task 4: Measure markers of endothelial integrity and assess plasma composition for extracellular vesicles: 0%

Subtask 1 (Aim 2b. To determine the hemostatic potency of EVs present in the transfused FFP units and relate this potency to alterations in the parameters assessing endotheliopathy in each patient): Extracellular vesicle measurements in blood samples and FFP satellites/samples **0%**

Subtask 2 (Aim 2a. To evaluate the level of “endotheliopathy” (endothelial dysfunction) at baseline and after plasma transfusion): Marker protein level quantification including CD-138, sTM, neutrophil elastase-antitrypsin complex, sP-selectin (blood samples and FFP

satellites/samples) **0%**

*Subtask 3 (Aim 2a): Vascular leakage quantification including fibrinogen, α 2-macroglobulin, VEGF, and ceruloplasmin (Saliva) **0%***

Milestone(s) Achieved: Endothelial function data obtained and integration with clinical and other data

Specific Aim 3: To assess the trajectory of clot stability in burn patients undergoing a resuscitation protocol that includes plasma

Major Task 5 (3a. To evaluate the relationship between thrombin generation intensity (procoagulant potential) and clot stability in the burn patient receiving plasma resuscitation. 3b. To determine whether observed changes in clot stability are solely derived from the transfused product): Measure markers and assessments of coagulation **10%**

*Subtask 1: Mine transcriptome data for related differential gene expression (see protein markers) **0%***

*Subtask 2: Marker protein level quantification and functional assays including α -TAT, fibrin monomer, D-Dimer, PAI-1, factors II, V, VII, VIII, IX, X, AT, TFPI, PC, XI, XII, plasminogen, FXIII, TAFI, C1 esterase inhibitor, etc. (blood samples and FFP) **0%***

*Subtask 3: Data analysis and integration **0%***

Milestone(s) Achieved: Coagulation data obtained and integration with clinical and other data

Major Task 6: Data analysis and integration using systems biology approaches **0%**

*Subtask 1: Analyze data and integrate assay results, clinical data and outcomes, functional assay results, and relationships between FFP and patient samples **0%***

*Subtask 2: Produce reports and manuscripts **0%***

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:

- 23 patients were enrolled into this study during this year.
- Continuing review approved by local IRB 1/26/2021 and HRPO 2/10/2021

- Added TEG in addition to ROTEM to analyze clot stability
- First shipment sent to University of Vermont to being assay completion on September 24, 2021

Key Results/Outcomes Findings:

- Nothing to Report at this time

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.

Development of manual of procedures and practical real time sample processing guides have allowed for training of 14 staff members (with varying degrees of laboratory experience) to become proficient in simple sample processing, real time thromboelastography and rotational thromboelastometry, platelet aggregometry, and bar coded freezer management. This has been accomplished through group and one-on-one training.

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 it is expected that patient enrollment shall be completed. Then the focus of the research team will move towards sample shipping and assay completion as well as

entry and auditing of the clinical data.

Once more assay information is available the team will begin initial data analysis.

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.

Minor changes were made to the inclusion and exclusion criteria of the study to ensure that if a subject's initial TBSA is $\geq 20\%$ but then later revised to be less than 20% may be enrolled without protocol deviation. This was done in recognition that the initial estimate of the TBSA may differ from final determination.

The research team received funding (outside of the named grant) to purchase a thromboelastography machine. This was added as a tool to provide additional data that will aid in completing Major Task 5.

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

Nothing to Report

Significant changes in use or care of vertebrate animals

Not Applicable.

Significant changes in use of biohazards and/or select agents

Not Applicable.

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 at this time.

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 at this time.

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 at this time.

- **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 at this time.

- **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 at this time.

- **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 at this time.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name: Jeffrey W. Shupp, MD
Project Role: Principal Investigator
Nearest person month worked: 1
Contribution to Project: Dr. Shupp provided overall oversight and guidance related to appropriateness of subject enrollment and removed subjects from continued sample collection if milestones were not met.

Name: Lauren Moffatt, PhD
Project Role: Lab and Admin Manager
Nearest person month worked: 1
Contribution to Project: Dr. Moffatt provided laboratory oversight and assisted with platelet aggregometry troubleshooting. She generated required reporting for the award along with Ms McLawhorn.

Name: Melissa McLawhorn
Project Role: Project Manager
Nearest person month worked: 3
Contribution to Project: Ms. McLawhorn provided clinical oversight and assistance for all aspects of protocol implementation including subject enrollment, sample processing, data monitoring, and ICF completion. She interfaces with regulatory personnel as necessitated including securing the continuing review and HRPO updates. She has worked with Dr. Moffatt to generate required reporting and updated the protocol, manual of procedures, and processing protocol as needed. She maintains and ensure the on-call calendar for the study team member

Name: Sarah Burkey
Project Role: Clinical Research Coordinator
Nearest person month worked: 4
Contribution to Project: Ms. Burkey monitored for eligible subjects, performed informed consents, processed samples, and collected clinical data. She is working with Ms. McLawhorn on data monitoring. She also packed and sent the first shipment of samples to Dr. Orfeo.

Name: Nataly Requeno
Project Role: Clinical Research Coordinator
Nearest person month worked: 2
Contribution to Project: Ms. Requeno monitored for eligible subjects, performed informed consents, processed samples, and collected clinical data.

Name: Mounica Bevara
Project Role: Clinical Research Coordinator
Nearest person month worked: 2
Contribution to Project: Ms. Bevara monitored for eligible subjects, performed informed consents, processed samples, and collected clinical data.

Name: Cara Delatore
Project Role: Clinical Research Assistant → Clinical Research Coordinator
Nearest person month worked: 3
Contribution to Project: Ms. Delatore monitored for eligible subjects, performed informed consents, processed samples, and collected clinical data. She assisted Ms. McLawhorn on integrating the TEG machine into the sample processing plan. She is working with Ms. Burkey on data monitoring.

Name: Lou'ay Hussein
Project Role: Lab Technician
Nearest person month worked: 2
Contribution to Project: Mr. Hussein monitored for eligible subjects, performed informed consents, processed samples, and collected clinical data.

Name: Connor Scannell
Project Role: Lab Technician
Nearest person month worked: 1
Contribution to Project: Mr. Scannell monitored for eligible subjects, performed informed consents, processed samples, and collected clinical data.

Name: Mary Oliver
Project Role: Lab Technician

Nearest person month worked: 2

Contribution to Project: Ms. Oliver monitored for eligible subjects, performed informed consents, processed samples, and collected clinical data.

Name: Thomas Orfeo, PhD

Project Role: UVM subcontract Principal Investigator

Nearest person month worked: 1

Contribution to Project: Dr. Orfeo has been initiating assay protocols and experimental systems at UVM. He has received the first shipment from MWHC of samples and is preparing to start assays.

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.

Study team has received additional support in the terms of contracted industry research since the last reporting period.

Additional funding has been added on a sub-award from BARDA via Philips and OHSU. No changes in effort are expected as a results of the new funding.

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

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.