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TITLE: Novel Dried Cryoprecipitate-Based Intervention to Improve Outcomes from Trauma and Hemorrhagic Shock: Applicability for Multidomain Operations

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U.S. Army Medical Research and Development Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT: The major objective of this effort is to define the role of a five day shelf life pathogen reduced cryoprecipitate (5PRC) and lyophilized cryoprecipitate (LPRC) using 2 different small animal models of hemorrhagic shock (HS) to examine the effect of these novel products on both hemostasis and endothelial protection. The long-term goal is FDA approval of these products for clinical and field use after HS. We HYPOTHESIZE that pathogen reduced cryoprecipitate-based interventions will decrease both early hemorrhagic deaths and later MOF through their dual effects on hemostasis and endothelial stability. To test this hypothesis, the early use of LPRC and 5PRC will be compared to conventional cryoprecipitate (CC), fresh frozen plasma (FFP) and standard of care Lactated Ringers (LR) in two different rodent models of trauma/HS applicable for multi-domain operations in the following specific aims: SA1. Determine the effect of early cryoprecipitate on hemostasis, organ function, and mortality in a short-term mouse model of trauma and uncontrolled hemorrhage (UCH). A well-established mouse liver transection model of UCH will be utilized followed by resuscitation with the described blood products or LR and compared to sham animals. Hemostasis, coagulation, lung function, endothelial integrity and short-term mortality will be assessed. SA2. Determine the effect of early cryoprecipitate on endothelial protection, organ failure and mortality in a mouse model of sustained hypotensive resuscitation. Our established mouse model of trauma/HS and sustained hypotensive resuscitation with the described blood products or LR and compared to shams. Following pronged hypotensive resuscitation (PHR) animals will be followed for 2 days to track survival.

15. SUBJECT TERMS
Hemorrhagic shock, prolonged hypotensive resuscitation, cryoprecipitate, endotheliopathy of trauma, pathogen reduced 5-day shelf life cryoprecipitate, pathogen reduced lyophilized cryoprecipitate

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The major ***objective*** of this effort is to define the role of a five day shelf life pathogen reduced cryoprecipitate (5PRC) and lyophilized cryoprecipitate (LPRC) using 2 different small animal models of hemorrhagic shock (HS) to examine the effect of these novel products on both hemostasis and endothelial protection. The ***long-term goal*** is FDA approval of these products for clinical and field use after HS. We ***HYPOTHESIZE*** that pathogen reduced cryoprecipitate-based interventions will decrease both early hemorrhagic deaths and later MOF through their dual effects on hemostasis and endothelial stability. To test this hypothesis, the early use of LPRC and 5PRC will be compared to conventional cryoprecipitate (CC), fresh frozen plasma (FFP) and standard of care Lactated Ringers (LR) in two different rodent models of trauma/HS applicable for multi-domain operations in the following ***specific aims: SA1***. ***Determine the effect of early cryoprecipitate on hemostasis, organ function, and mortality in a short- term mouse model of trauma and uncontrolled hemorrhage (UCH).*** A well-established mouse liver transection model of UCH will be utilized followed by resuscitation with the described blood products or LR and compared to sham animals. Hemostasis, coagulation, lung function, endothelial integrity and short-term mortality will be assessed. ***SA2. Determine the effect of early cryoprecipitate on endothelial protection, organ failure and mortality in a mouse model of sustained hypotensive resuscitation.*** Our established mouse model of trauma/HS and sustained hypotensive resuscitation with the described blood products or LR and compared to shams. Following pronged hypotensive resuscitation (PHR) animals will be followed for 2 days to track survival. Lung specific indicators of injury and function, endothelial integrity, leak and activation measured along with biomarkers of kidney and liver injury. The proposed research and downstream investigations will improve treatment of HS by providing critical information about cryoprecipitate-based resuscitation that would be of benefit to both military and civilian populations.

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

Hemorrhagic shock, prolonged hypotensive resuscitation, cryoprecipitate, endotheliopathy of trauma, pathogen reduced 5-day shelf life cryoprecipitate, pathogen reduced lyophilized cryoprecipitate

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.

Specific Aim 1. Determine the effect of early cryoprecipitate on hemostasis, endothelial protection, organ(lung) function, and mortality in a short term mouse model of trauma and uncontrolled hemorrhage (UCH)	**Timeline**	**Site 1**
Major Task 1	Months	
Subtask 1. Obtain local IACUC approval (estimated total number 159)	0-2	Completed
Subtask 2. Obtain ARUCO approval	0-4	Completed
Milestone Achieved: HRPO/ACURO Approvals	4	*Completed*
Major Task 2		
Subtask 1 Develop/optimize mouse model UCH (n=10)	4	Completed
Subtask 2. Complete mouse surgeries UCH (n=72)	4-10	completed
Subtask 3. Coagulation, hemostasis, shed syndecan	10-12	completed
Subtask 4 Lung histology, MPO, syndecan immunostaining and BAL protein	10-12	completed
Subtask 5: Lung VE-cadherin and vWF	10-12	completed
Subtask 6: Data Analysis	13-14	In progress
Milestone(s) Achieved: Completion of SA1	14	
Specific Aim 2. SA2. Determine the effect of early cryoprecipitate on endothelial protection, organ failure and mortality in a mouse model of sustained hypotensive resuscitation (SHR).		
Major Task 3		
Subtask 1 Develop/optimize mouse model SHR (n=5)	12	Completed
Subtask 2. Complete mouse studies SHR (n=72)	13-20	completed
Subtask 3. Lung histology, MPO, syndecan, Martius Scarlet Blue staining, and BAL protein	20-23	In progress
Subtask 4. Lung VE-cadherin and vWF	20-23	In progress
Subtask 5. Small bowel histology	20-23	In progress
Subtask 7 Serum biomarkers of renal and liver injury	20-23	In progress
Subtask 7: Data analysis	23-24	In progress
Milestone(s) Achieved: Completion of SA2	24	
Major Task 3		
Subtask 1. Write abstracts/posters/manuscripts	23-24	
Milestone(s) Achieved: Results dissemination: manuscript and abstracts publications and presentations	24	

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.

Specific Aim 1. Major Task 2. <u>Methods for Modified protocol</u>: Animals underwent isoflurane anesthesia then placement of femoral artery and vein catheters. A crush injury to the contralateral limb and a mid-shaft tibia fracture was performed using a surgical clamp. This will be done by extending the extremity, cleansing it with alternating scrubs of betadine and 70% ethanol 3 times. The middle of the tibia was placed over a sterilized blunt edge then manual pressure applied until a transverse fracture occurred. Next a Kelly clamp was placed along the length of the gastrocnemius muscle and tightened by closing it for 3 clicks. The tibia and gastrocnemius were not exposed for this procedure. It remained in place for 30 minutes. A laparotomy was then performed and the entire length of the bowel examined. Pre-weighed sterile gauze was placed in the lower quadrants to collect shed blood, then a liver laceration of 75% of the left lobe was performed. The laparotomy was closed quickly using sutures. Additional blood was removed/returned using femoral catheter to maintain MAP at 35 +/- 5. At 60 minutes, the mice were resuscitated with either 5 day shelf-life pathogen reduced cryoprecipitate(5PRC) or lyophilized pathogen reduced cryoprecipiate (LPRC) and compared to conventional cryoprecipitate (CC), fresh frozen plasma (FFP), or Lactated Ringers to maintain a MAP of 55+/- 5 At 3 hours the mice were euthanized by cardiac puncture. Blood and tissue was collected.

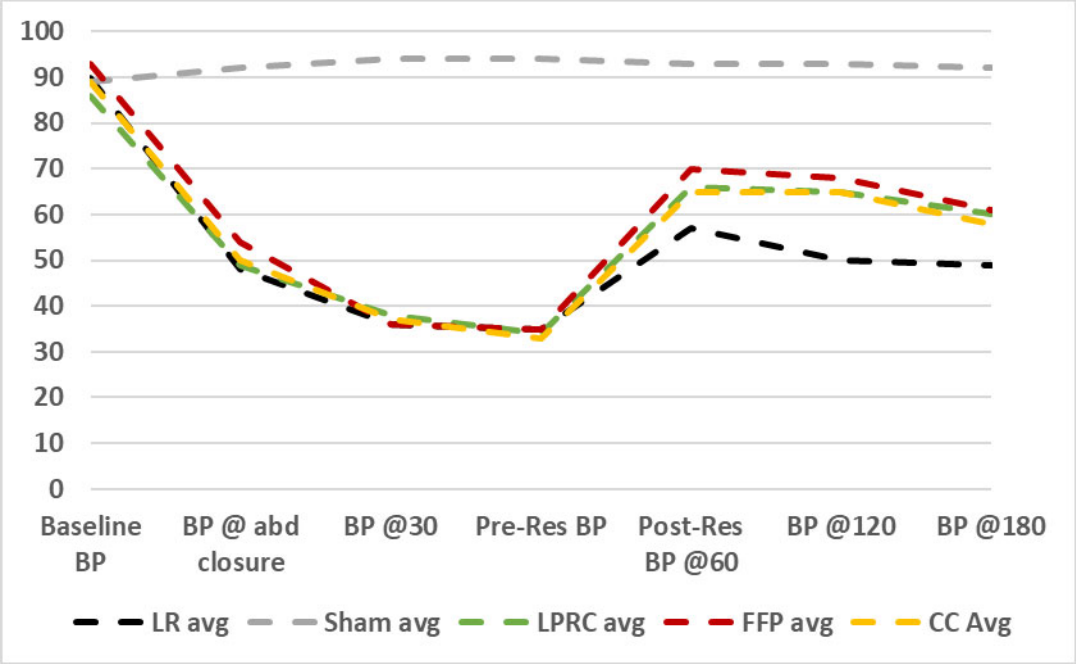
Results:

Eighty-six mice were used for this set of experiments. Overall mortality was 26%, with individual experimental groups results shown below. There is no significant difference in mortality between the resuscitation groups (Chi-square). The volume of resuscitation need to maintain SHR was higher for LR than the FFP or cryo groups. Blood loss from the liver injury was similar. We have learned that with this model of uncontrolled hemorrhage, blood loss is rapid but brief (less than five minutes), thus not allowing the ability to determine hemostasis differences between groups.

Group	Total sample size	Mortality (%)	Volume resuscitation (ul, ml/kg)	Baseline BP (mmHg)	Pre-resuscitation BP (mmHg)	BP at conclusion (mmHg)	Total blood loss (ml)
Sham	17	0	N/A	89±8	N/A	92±5	
Lactated Ringers	15	5 (33%)	1270±340 (43±10)	90±14	35±5	35±17	836±178
FFP	14	3 (14%)	364±106 (11±3)	93±9	35±4	56±16	868±205

Regular Cryo	15	5 (33%)	337±108 (11±4)	89±10	33±5	58±6	888±168
Long shelf 5-day cryo	12	5 (42%)	515±150 (18±6)	90±13	35±4	54±16	916±218
Lyocryo	13	4 (31%)	481±156 (16±5)	86±8	34±6	56±12	913±217

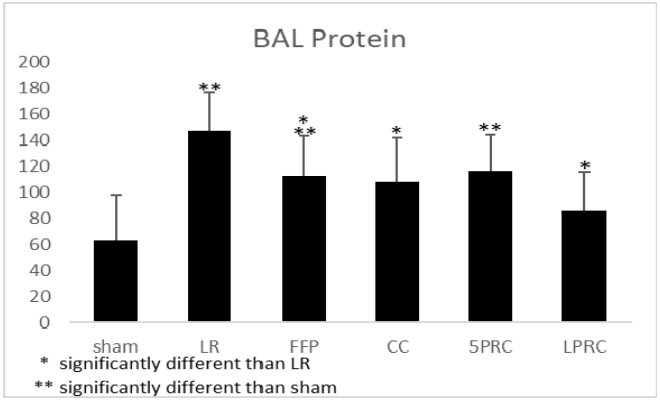
Blood pressure over time is displayed below.



There was no significant difference in MAP between groups at baseline or during the shock periods. At 60 minutes post-resuscitation MAP was higher in FFP compared to LR, at 120 minutes MAP was higher in the FFP, CC and LPRC vs LR group, by 180 minutes after resuscitation, all experimental groups were comparable (ANOVA with Tukey post-hoc test for multiple comparisons corrections).

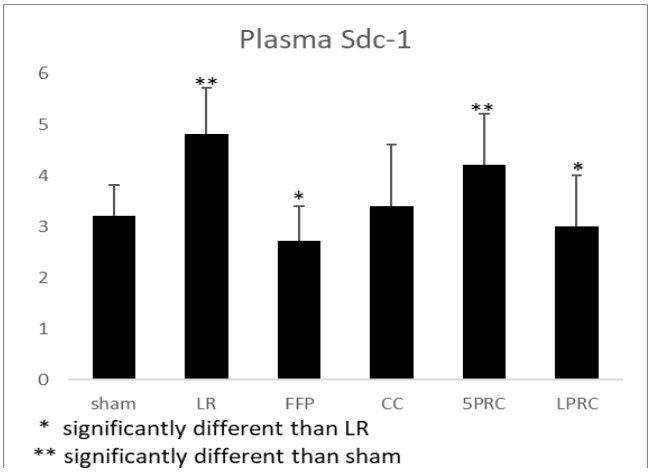
Analysis:

Endotheliopathy



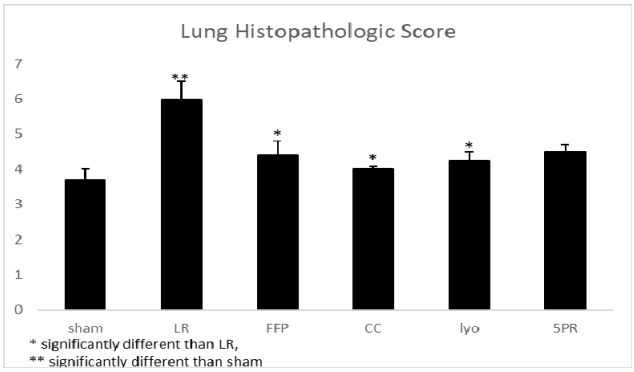
BAL protein is used an indicator of **permeability,** a key component of endotheliopathy. LR significantly increased permeability that was reduced by FFP, CC and LPRC.

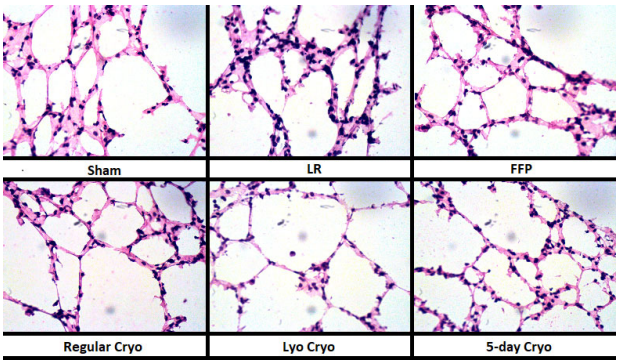
Plasma syndecan is a known biomarker for endotheliopathy. LR significantly increases shed syndecan-1 ectodomain, which was reduced by FFP and LPRC

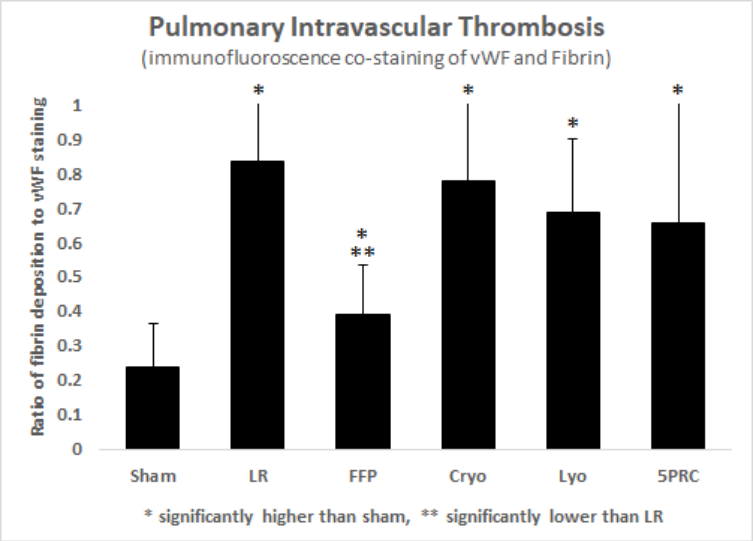


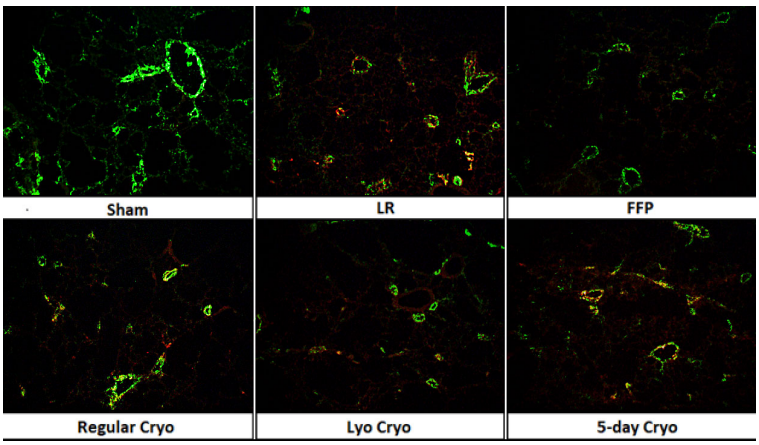
Tissue injury:

We next examined **lung histopathology** as an indicator of tissue injury. LR significantly increased lung injury which was reduced by FFP, CC and LPRC.



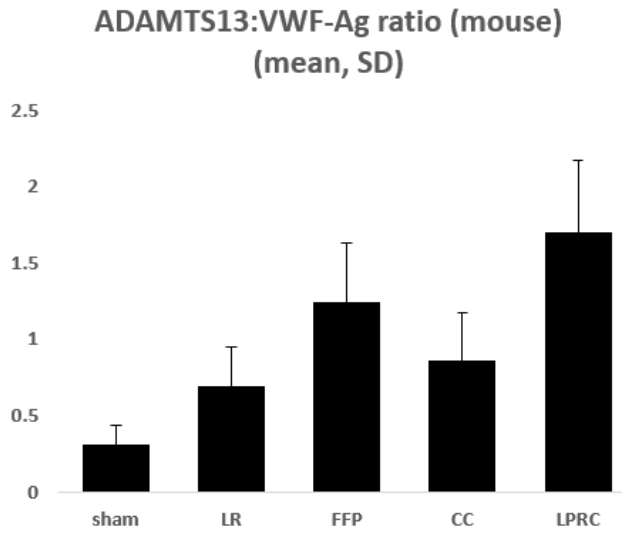


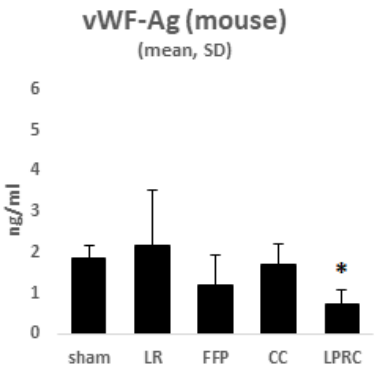


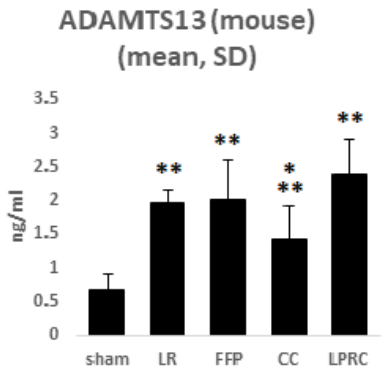


Pulmonary microvascular thrombosis (MVT) was also assessed by counterstaining green for VWF to identify endothelial cells and red for fibrin. Interestingly, all the groups increased MVT but most striking was that all 3 cryo groups were comparable to LR. Two different individuals performed staining and quantification and used slightly different techniques with the same conclusions. This finding was not associated with indices of endotheliopathy or tissue injury as shown above. We thought this might be due to the fact that the cryo products were inducing a hypercoagulable state. We assessed coagulopathy using a thrombin-antithrombin assay (TAT) but there was there was no significant difference between resuscitation groups (Sham 1.3±0.7, LR 2.1±0.6, FFP 2.1±0.6, CC 2.5±0.4, LPRC 2.2±0.8).

To further examine the potentially protective effects of the cryoprecipitate products on the endothelium, we measured both VWF and ADAMTS13, its cleaving enzyme.







The increase in the ADAMTS13:VWF ratio in the LPRC is quite interesting and reason unclear. As shown, this is being driven by an intrinsic increase in mouse ADAMTS13. In an attempt to explain this, we examined synthesis of ADAMTS13 in the liver, as this is the site of production. There was no change in mRNA between groups. This is not surprising as the half-life of ADAMTS13 is 2-4 days and our experiment lasted only several hours. There are several reports of ADAMTS13 being found in endothelial cells. Whether it is potentially able to be released preformed has not been investigated.

To ensure we were not measuring human ADAMTS13 with our mouse assay: We measured human VWF and ADAMTS13 in the mouse blood and detected human NO VWF or ADAMTS 13 in the shams and LR groups, suggesting there is no cross-reactivity between assays. Additionally, LPRC should theoretically have no or trace ADAMTS 13 as it is found in plasma and not in isolated cryoprecipitate. Conventional cryo is suspended in a small amount of plasma for administration but lyophilized cryo is resuspended in sterile water. We are going to measure the amount of both mouse and human VWF and ADAMTS13 in human FFP, CC, and LPRC. First this has not been done by the company for the pathogen reduced products they supplied us with (CC and LPRC) and second, we want again verity the mouse assay does not cross react with human assay. We have contact the companies for help with cross-reactivity but responses are pending.

SA 2. Major Task 3:

Methods: C57BL/6J mice 12-16 weeks old and 22-25 grams underwent anesthesia with inhaled oxygen and isoflurane. A rectal thermometer was inserted and mice placed on a heating pad. The femoral artery was dissected and cannulated for continuous blood pressure monitoring and blood draws for solution infusion. Baseline blood pressure was monitored and trauma mimicked by performing a 2 cm midline laparotomy, manipulating the bowel, then closing the abdomen. Blood was slowly withdrawn through the arterial catheter until MAP of 35mmHg was achieved. After 90 minutes, mice were resuscitated to achieve a MAP of 55-60mmHg. Sustained hypoptensive resuscitation was carried out for a total of 6 hours. Catheters were then removed, incisions closed, and the animals awoken from anesthesia. At 72 hours from the initiation of shock, animals were euthanized and blood and tissue harvested.

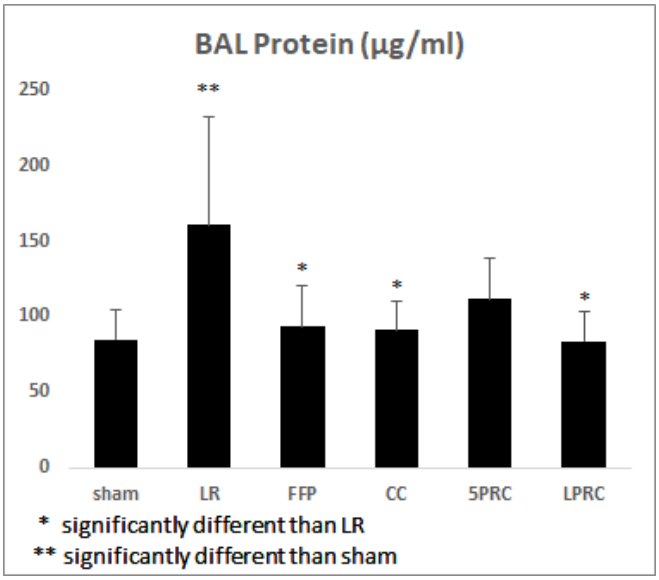
Subtask 2; Animal surgeries

Group	Total sample size	Mortality (%)	Volume resuscitation (ul, ml/kg)	Baseline BP (mmHg)	Pre-resuscitation BP (mmHg)	BP at 6 hr (mmHg)	Total blood loss (ml)	BP at POD 3 (mmHg)

Sham	8	0	N/A	100±7	N/A	95±5	N/A	105±10
Lactated Ringers	12	4 (33%)	675±261 (25±10)	92±8	34±4	55±6	738±111	77±12
FFP	11	3 (27%)	300±103 (11±3)	93±10	33±4	68±12	694±53	86±12
Regular Cryo	10	2 (20%)	188±70 (7±3)	94±9	33±4	68±9	788±65	86±19
Lyocryo	9	1 (11%)	300±117 (11±4)	89±7	33±4	74±8	713±114	81±10

We have not completed statistical analysis on the data above but its clear that similar to our short term experiments in SA1, the volume of resuscitation is much higher with LR.

Assays: We have just begun analysis.



Bronchoalveolar lavage protein as an indicator of lung permeability: Results demonstrate a significant increase in permeability by LR but a reduction in permeability following resuscitation with FFP, conventional cryo (CC), and lyocryo (LPRC). Although there was a trend towards a decrease with 5day pathogen reduced cryo (5PRC), it was not significant.

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.

We will continue to work on the assays for SA2 Major Task 3. Hope to submit a manuscript from data on SA1.

4. **IMPACT:** D*escribe 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.*

There are clinical studies looking at the early use of cryoprecipitate. Results of this study suggest benefit in reducing the endotheliopathy of trauma.

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:*

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

SA1. As discussed prior, we have encountered difficulties in interpreting our systemic results as we used a human plasma in a rodent model and we have realized we need to understand what is secreted from mice into the systemic circulation vs what is present in the plasma from the products we administered. We have been able to obtain ELISAs for all these assays except to detect the pathologic VWF

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

Nothing to report

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

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

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

The work from Major Task 2 using the original model was presented at the AAST meeting as a poster in September 2021.

- **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

4. 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: Rosemary Kozar
Project Role: Principal Investigator
Nearest person month worked: 3.0 calendar month
Contribution to Project: Designed study, oversees all aspects and conduct of the study

Name: Feng Wu
Project Role: Research Associate
Nearest person month worked: 2.4 calendar months
Contribution to Project: Assisting with assays

Name: Ahmad Zeineddin
Project Role: Post-Doctoral Fellow
Nearest person month worked: 12.0 calendar months
Contribution to Project: Responsible for the overall conduct of studies including performing all animal surgeries and assays.

Name: Brooke Dorman
Project Role: Laboratory Assistant
Nearest person month worked: 0.6 calendar months
Contribution to Project: Assisting with tissue sectioning and assays

Name: Shibani Pati
Project Role: Co-Investigator
Nearest person month worked: 1.0 calendar months
Contribution to Project: Advising and assisting in trouble shooting

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.

New:
03/01/2022 – 01/31/2026 Kozar (Co-PI) 25% effort
Trauma and Shock-Induced Microvascular Dysregulation and Coagulopathy Sponsor

Closed:
09/15/2017 – 03/14/2022 Kozar (PI) 5% effort
Dried Plasma to Improve Outcomes in Polytrauma

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.*

Organization Name: The Regents of the University of California, San Francisco (Dr. Shibani Pati)
Location of Organization: San Francisco, CA
Partner's contribution to the project (identify one or more):

- Other: Advisory

5. **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://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

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

6. **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.*