AWARD NUMBER: W81XWH-18-1-0536

TITLE: Plasmin Therapy to Prevent Post-Traumatic Heterotopic Ossification in the Upper Extremity After Severe Injury

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Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of this prospective animal study is to investigate new treatments to improve upper extremity joint function and prevent heterotopic ossification (HO, pathologic bone formation in muscle) follow severe injury. Plasmin is a critical reparative protease, essential for tissue regeneration following injury. The work proposed in this application will delineate the ideal timing for prophylactic plasmin therapy needed for clinical trials in both military and civilian trauma patients at risk for developing HO and associated impaired joint function. If our overarching hypothesis is proven true, the clinical impact is of most importance in the upper extremity as even partial prevention of a shoulder or elbow joint contracture can provide a wounded soldier or civilian with independence in activities of daily living. Importantly, as we have established that plasmin is essential both for preventing HO and promoting fracture repair/bone health, this would be the first therapy that does not compromise bone biology in order to prevent HO.

15. SUBJECT TERMS
Heterotopic Ossification, Upper extremity function, joint contracture

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Unclassified	Unclassified	Unclassified	Unclassified	12	**19b. TELEPHONE NUMBER**

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1. INTRODUCTION:

It's estimated that over 50% of combat-related injuries sustained by military personnel affect the musculoskeletal system, with musculoskeletal injuries being one of the most common reasons for medical discharge. Heterotopic ossification (HO) is a significant source of morbidity related to these injuries due to loss of joint and muscle function and chronic pain. HO of the elbow and shoulder joints hinders normal joint function and the ability to perform daily activities. Combat-related amputation from injuries to the extremities can also increase the risk of HO development post-surgery. Chronic musculoskeletal conditions not only prevent return to duty, but they can also increase the risk for future injuries. As such, combat-related HO presents a substantial medical burden to the military with long-term consequences.

Treatments for HO include prophylactic drugs, surgical intervention, physical therapy, and radiation therapy, but all of these treatments either lack efficacy or instigate significant adverse effects. Surgical removal of HO is effective, but this is only beneficial if intervention occurs after the HO has matured and it institutes a high risk of hemorrhage and infection, both of which may increase morbidity and medical costs. While prophylactic NSAID therapy remains largely ineffective for the prevention of HO, bisphosphonate therapy, while effective, negatively affects fracture healing and bone remodeling. As such, an effective prophylactic therapy that does not interfere with bone healing or maintenance will not only prevent HO and long-term sequelae, but it will also circumvent the medical complications associated with the current therapeutic interventions.

The overall objective of this prospective animal study is to investigate new treatments to improve upper extremity joint function and prevent HO follow severe injury. Plasmin is a critical reparative protease, essential for tissue regeneration following injury. Findings from our laboratory have demonstrated that in severely injured patients, such as individuals experiencing burn injuries, plasmin is depleted in relation to the severity of injury (as measured by total body surface area burned). Aligning with these clinical results, we observed a marked depletion of plasmin activity in our murine model of thermal injury. Furthermore, when mice received a concomitant burn and tissue injury to their elbow, we observed HO formation and impaired elbow function, akin to results observed in genetically plasminogen deficient animals.

From these results, this proposal is focused on the application of plasmin therapy, as a means to reduce HO formation and improve upper extremity function following injury. Specifically, the work proposed in this application will delineate the ideal timing for prophylactic plasmin therapy. The proposed research will be conducted using a validated murine skeletal muscle injury at the elbow which results in calcification around the elbow with functional deficits of that upper extremity.

If our overarching hypothesis is proven true, the clinical impact is of most importance in the upper extremity as even partial prevention of a shoulder or elbow joint contracture can provide a wounded soldier or civilian with independence in activities of daily living. Importantly, as we have established that plasmin is essential both for preventing HO and promoting fracture repair/bone health, this would be the first therapy that does not compromise bone biology in order to prevent HO.

The Aims to be examined include:

Aim 1: Determine the therapeutic window of restoring plasminogen consumed by thermal injury with recombinant plasminogen to prevent upper extremity heterotopic ossification and loss of function.

Aim 2: Determine the therapeutic window of enhancing plasmin activity by targeting plasmin's inhibitor (alpha2-anti-plamsin) to prevent upper extremity heterotopic ossification and loss of function.

Aim 3: We postulate that utilizing both methods, within their critical therapeutic windows determined in Aim 1 and 2, will provide the most efficacious treatment that prevents elbow heterotopic ossification and loss of function after a severe thermal injury with a concomitant injury of the elbow.

2. KEYWORDS:

Heterotopic Ossification, Upper extremity function, joint contracture, plasminogen, elbow

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: **Determine the optimal timing of enhancing plasmin activity by targeting its inhibitor α2AP that i) restores plasmin activity, ii) prevents HO and elbow joint contracture.**	**Timeline**	**Site 1**	**Site 2**
Major Task 1: Conduct muscle injury model with/without a2AP ASO administration	**Months**	**Site 1**	**Site 2**
Subtask 1: Obtain ACURO approval	1-3	Dr. Schoenecker	
Subtask 2: Obtain IACUC approval	1-3	Dr. Schoenecker	
Subtask 3: Treatment administered beginning at 0,1,2,3,4,5,6, or 7 days post injury.	3-9	Dr. Schoenecker (80 mice total)	
Subtask 4: Synthesis of fibrin targeting peptide (FTP) for weekly in vivo imaging of fibrin resolution by plasmin	1-6		Dr. McCarthy
Milestone Achieved: Local IACUC and ACURO Approval	3	Dr. Schoenecker	
Milestone: Synthesis of fibrin targeting peptide completed	6		Dr. McCarthy
Major Task 2: Longitudinal Assessment of HO	**Months**	**Site 1**	**Site 2**
Subtask 1: Radiographic Analysis weekly: 7, 14, 21, and 28 DPI	3-9	Dr. Schoenecker	
Subtask 2: MicroCT analysis Endpoint: 28 DPI.	6-12	Dr. Schoenecker	
Subtask 3: Histological Analysis Endpoint: 28 DPI.	6-12	Dr. Schoenecker	
Milestone(s) Achieved: Completed HO assessment with a2AP ASO treatment	12	Dr. Schoenecker	

Major Task 3: Longitudinal Assessment of Elbow Function	**Months**	**Site 1**	**Site 2**
Subtask 1: Grip Strength Analysis weekly: 7, 14, 21, 28 DPI	4-9	Dr. Schoenecker	
Subtask 2: Wire Hang Analysis weekly: 7, 14, 21, and 28 DPI	4-9	Dr. Schoenecker	
Subtask 3: Treadscan Analysis weekly: 7, 14, 21, and 28 DPI	4-9	Dr. Schoenecker	
Milestone Achieved: Completed elbow function assessment with a2AP ASO treatment	9	Dr. Schoenecker	
Major Task 4: Longitudinal Assessment of Plasminogen Levels	**Months**	**Site 1**	**Site 2**
Subtask 1: Serologic Analysis weekly: 7, 14, 21, and 28 DPI	4-12	Dr. Schoenecker	
Subtask 2: Weekly assessment of fibrin resolution by plasmin using in vivo imaging of FTP: 7, 14, 21, and 28 DPI	4-9	Dr. Schoenecker	
Milestone Achieved: Completed assessment of plasminogen levels and plasmin activity with a2AP ASO treatment	12	Dr. Schoenecker	
Major Task 5: Data Analysis	**Months**	**Site 1**	**Site 2**
Subtask 1: Data Analysis	6-12	Dr. Schoenecker	
Milestone Achieved: Completion of all data collection and analysis within Aim 1	12	Dr. Schoenecker	
Specific Aim 2: Determine the optimal timing of restoring plasminogen by administering recombinant plasminogen that i) restores circulating plasminogen levels, ii) prevents heterotopic ossification (HO) and elbow joint contracture	**Timeline**	**Site 1**	**Site 2**
Major Task 1: Conduct muscle injury model with/without recombinant plasminogen administration	Months		
Subtask 1: Treatment administered at 0,1,2,3,4,5,6, or 7 days post injury. 5 mice per group.	12-18	Dr. Schoenecker (80 mice total)	

Subtask 2: Synthesis of FTP	12-18		Dr. McCarthy
Milestone Achieved: Completion of model with recombinant plasminogen administration and FTP synthesis	18	Dr. Schoenecker	
Major Task 2: Longitudinal Assessment of HO	**Months**	**Site 1**	**Site 2**
Subtask 1: Radiographic Analysis weekly: 7, 14, 21, and 28 DPI	12-18	Dr. Schoenecker	
Subtask 2: MicroCT analysis Endpoint at 28 DPI.	15-21	Dr. Schoenecker	
Subtask 3: Histological Analysis Endpoint at 28 DPI.	15-21	Dr. Schoenecker	
Milestone Achieved: Completion of HO assessment following recombinant plasminogen administration	21	Dr. Schoenecker	
Major Task 3: Longitudinal Assessment of Elbow Function	**Months**	**Site 1**	**Site 2**
Subtask 1: Grip Strength Analysis weekly: 7, 14, 21, and 28 DPI	13-18	Dr. Schoenecker	
Subtask 2: Wire Hang Analysis weekly: 7, 14, 21, and 28 DPI	13-18	Dr. Schoenecker	
Subtask 3: Treadscan Analysis weekly: 7, 14, 21, and 28 DPI	13-18	Dr. Schoenecker	
Milestone Achieved: Completed elbow function analysis following recombinant plasminogen administration	18	Dr. Schoenecker	
Major Task 4: Longitudinal Assessment of Plasminogen Levels	**Months**	**Site 1**	**Site 2**
Subtask 1: Serologic Analysis weekly: 7, 14, 21, and 28 DPI	15-21	Dr. Schoenecker	
Subtask 2: Weekly assessment of fibrin resolution by plasmin using in vivo imaging of FTP: 7, 14, 21, and 28 DPI	13-18	Dr. Schoenecker	
Milestone Achieved: Completed assessment of plasminogen levels and plasmin activity with recombinant plasminogen	21	Dr. Schoenecker	

Major Task 5: Data Analysis			
Subtask 1: Data Analysis	16-24	Dr. Schoenecker	
Milestone Achieved: Completion of all data collection and analysis within Aim 2	24	Dr. Schoenecker	Dr. McCarthy
Specific Aim 3: Determine the optimal timing and duration of administration of a2AP ASO + recombinant plasminogen that prevents HO and elbow joint contracture following muscle injury.	**Timeline**	**Site 1**	**Site 2**
Major Task 1: Conduct the muscle injury model with/without a2AP ASO + recombinant plasminogen administration	**Months**	**Site 1**	**Site 2**
Subtask 1: Treatment administered based on optimal dosing points determined in aims 1 & 2. 5 mice per group.	24-30	Dr. Schoenecker (80 mice total)	
Subtask 2: Synthesis of FTP	24-30		Dr. McCarthy
Milestones Achieved: Completion of muscle injury model with combined dosing of therapeutics	30	Dr. Schoenecker	
Major Task 2: Longitudinal Assessment of HO.	**Months**	**Site 1**	**Site 2**
Subtask 1: Radiographic Analysis weekly: 7, 14, 21, and 28 DPI	24-30	Dr. Schoenecker	
Subtask 2: MicroCT analysis Endpoint at 28 DPI.	27-33	Dr. Schoenecker	
Subtask 3: Histological Analysis Endpoint at 28 DPI.	27-33	Dr. Schoenecker	
Milestone Achieved: Completion of HO assessment following combined therapy	33	Dr. Schoenecker	
Major Task 3: Longitudinal Assessment of Elbow Function	**Months**	**Site 1**	**Site 2**
Subtask 1: Grip Strength Analysis weekly: 7, 14, 21, and 28 DPI	24-30	Dr. Schoenecker	
Subtask 2: Wire Hang Analysis weekly: 7, 14, 21, and 28 DPI	24-30	Dr. Schoenecker	

Subtask 3: Treadscan Analysis weekly: 7, 14, 21, and 28 DPI	24-30	Dr. Schoenecker	
Milestone Achieved: Completion of elbow function assessment following combined therapy	30	Dr. Schoenecker	
Major Task 4: Longitudinal Assessment of Plasminogen Levels			
Subtask 1: Serologic Analysis weekly: 7, 14, 21, and 28 DPI	27-33	Dr. Schoenecker	
Subtask 2: Weekly assessment of fibrin resolution by plasmin using in vivo imaging of FTP: 7, 14, 21, and 28 DPI	25-30	Dr. Schoenecker	
Milestone achieved: Completed assessment of plasminogen levels and plasmin activity with both plasminogen and a2AP ASO therapies	33	Dr. Schoenecker	
Major Task 5: Data Analysis and Manuscript Preparation			
Subtask 1: Data Analysis	30-36	Dr. Schoenecker	
Subtask 2: Manuscript Preparation	30-36	Dr. Schoenecker	Dr. McCarthy
Milestones Achieved: Completion of all data collection and analysis within Aim 3 and manuscript preparation of data collected from this proposal	36	Dr. Schoenecker	Dr. McCarthy

What was accomplished under these goals?

Milestone Achieved in 1st Year of Proposal:
Major Task 1, Subtask 1: Obtain ACURO Approval
Major Task 1, Subtask 2: Obtain IACUC Approval
Major Task 1, Subtask 4: Begin synthesis of FTP peptide
Major Task 1, Subtask 3: Begin experiments. Treatment administration a2AP ASO
Major Task 2, Subtask 1: Begin Radiographic analysis weekly.
Major Task 3, Subtask 1-3: Begin Functional Assessments- Grip Strength Analysis/wire hang/tredscan
Major Task 4, Sub task 1-2: Begin assessment of Plasminogen Levels

Milestones to be accomplished in Year 2:
Major Task 1, Subtask 4: Continue synthesis of FTP peptide
Continue Major Task 1, Subtask 3: Continue experiments. Treatment administration a2AP ASO

Continue Major Task 2, Subtask 1: Continue Radiographic analysis weekly.
Continue Major Task 3, Subtask 1-3: Continue Functional Assessments-
Continue Major Task 4, Sub task 1-2: Continue assessment of Plasminogen Levels
Major Task 5, Sub task 1: Begin data analysis
Specific Aim 2- Major Task 1: Obtain recombinant plasminogen from collaborators for use in model

COVID-19 has had a significant impact on this year's research goals due to personnel and experimental restrictions. While much has been done to minimize the impact of COVID-19 on this research, a delay in the number of experiments able to be completed was experienced

Specific Aim 2- Major Task 1: Shortly prior to restrictions being put into place for research due to COVID-19, we obtained an ample supply of recombinant plasminogen from collaborators for use in our model. As the lab enters into phase 2 (50% capacity), we anticipate moving forward on experiments proposed in Aims 1 and 3 in the coming months.

The overarching goal of this proposal is to examine therapeutics aim at i) prevent skeletal muscle calcification and 2) improving elbow function following traumatic injury. Through experiments conducted in year 1, we have demonstrated that a2AP ASO administration at the time of injury effectively reduced calcification of skeletal muscle surrounding the elbow. Yet, no marked difference in elbow function was observed given that all mice, intendent of burn application or therapy, heal well by 28DPI. For this reason, during the slowed research endeavors as a result of COVID-19, we improved our injury model to more effectively examine the therapeutic effect on skeletal muscle calcification and elbow function.

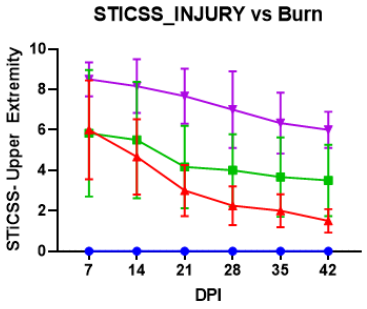
Previously, our lab has demonstrated that plasminogen, and its active form plasmin, is essential for protecting skeletal muscle from calcification and promoting muscle repair (PMID: 27530373). Ongoing clinical work by our laboratory (outside of this grant) has demonstrated that patients with severe burn injuries, plasminogen antigen levels and plasmin enzyme activity are both reduced relative to the severity of the burn injury. When a proportional amount of plasminogen is depleted in our mouse model (40-50%, Plasminogen (PLG) Heterozygous animals), this leads to marked skeletal muscle calcification following a focal muscle injury, that progresses to HO between 28 and 42 days post injury. For these reasons, we examined if upper extremity muscle injury in plasminogen heterozygous animals, with or without burn injury, would more effectively model muscle calcification with persistent diminishment in upper extremity function.

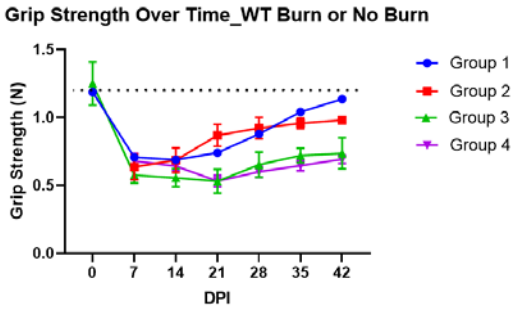
Four experimental groups were compared as part of this experiment: 1) PLG WT animals + upper extremity injury, 2) PLG WT animals + Burn + upper extremity injury, 3) PLG HET + Upper extremity injury, 4) PLG HET + Burn + Upper extremity injury.

When assessing soft tissue calcification (STiCSS), while no calcification was observed in the control group 1 (blue), marked calcification was observed in PLG WT mice following burn injury (Group 2, red). As previously observed, the calcification observed in group 2 at 7 days post injury regressed over 42 days post injury. When assessing PLG HET mice, following injury alone, marked calcification was observed at 7 DPI (Group 3, green). When burn was applied in combination, even greater calcification was observed at 7DPI (Group 4, purple). Contrary to WT

animals, the rate of regression was diminished in PLG HET mice +/- burn injury, resulting in persistent calcification and the formation of HO within skeletal muscle by 42 DPI.

When assessing upper extremity function, all mice experience comparable drops in grip strength by 7DPI, independent of burn injury. While WT function re-established to new WT levels over time (group 1 and 2, red and blue), grip strength remained diminished in all PLG HET mice, independent of burn injury (Group 3 and 4, green and purple).





Given these findings, we have worked with the award administrators program directors to shift all future experiments assessing therapeutics aimed at i) prevent skeletal muscle calcification and 2) improving elbow function following traumatic injury to PLG HET mice without burn injury. This change has been noted in our updated SOW. While calcification is greater when combined with burn injury, both burned and unburned PLG HET mice develop HO and no additional functional deficient was observed with the addition of burn injury.

Plasminogen deficient mice are already readably bred as part of our animal colony and available for use in these studies emergently, Furthermore, by moving away from the burn + upper extremity injury model to only a focal muscle injury, we will be able to 1) expediate experiments by examining more animals simultaneously to overcome time loss due to COVID in Year 2, 2) off set the slight increase in cost of breeding animals by being able to house 5 mice per cage, as opposed to individual housing required of the burn animals, and 3) produce more consistent results by removing the burn injury as a variable. Additionally, we have been approved to maintain our breeding colony going forward, independent of research restriction due to COVID-19 in the future. This is not true for ordering animals into facilities, as would be necessitated under our current model. Therefore, this modification in model provides us an extra level of protection from future shut down measures.

Finally, prior work by our laboratory has illustrated that a2AP ASO administered before injury effectively prevent muscle calcification in PLG HETs, aligning with results previously obtained in the burn model. Therefore, together, we anticipate this modification to our work to be conducted in PLG HET animals will be incredibly fruitful and an overall improvement to the present studies.

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

How were the results disseminated to communities of interest?
Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?
During the next reporting period, we plan to continue our studies investigating the therapeutic window in which a2AP ASO is effective at inhibit muscle calcification and the associated effects on upper extremity function in PLG HET animals. In addition to grip strength, we will be looking into new novel methods that may better reflect upper extremity function and translatability to human activities of daily living.

4. **IMPACT:**
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:**
Changes in approach and reasons for change
Due to the laboratory reducing staff and experiments in compliance with COVID-19 work restrictions, a slower rate of data generations and experimental analysis has been possible in year 2. In order to improve upon experimental outcome and expediate future work, we have gained approval to move all future experiments into PLG HET mice + an upper extremity injury model. The feasibility of this transition has been fully examined and discussed above.

Actual or anticipated problems or delays and actions or plans to resolve them
Aligning with COVID-19 restriction, we have been instructed to limit the number of new animals purchased and brought into our facility. This directly impacted this proposal. Furthermore, many parallel studies on going in the lab have been paused, resulting in a net gain of PLG HET mice available to this proposal. Therefore, to both improve the outcomes of this proposal, while simultaneously utilizing available resources, we conducted a pilot experiment to demonstrate the improve utility of PLG HET mice in this proposal. While restrictions are just now beginning to lift, the use of PLG heterozygous mice will allow for expediate and improved data gathering compared to prior proposed WT + Burn experiments.

Changes that had a significant impact on expenditures

COVID-19 has had a significant impact on this year's research goals due to personnel and experimental restrictions. While much has been done to minimize the impact of COVID-19 on this research, we did experience a delay in result production. As noted above, we have devised a feasible plan to limit future delays.

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
Not Applicable

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**
  Nothing to Report
  Journal publications. Nothing to Report
  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?

Commented [SM1]: Glenna to update

Name: *Jonathan G Schoenecker*
Project Role: *PI*
Researcher Identifier (e.g. ORCID ID): 0000-0002-3097-5496
Nearest person month worked: *2*
Contribution to Project: *Dr. Schoenecker oversaw the IACUC and ACURO submission process and directed the planning of upcoming experiments. Dr. Schoenecker worked with Dr. Moore-Lotridge to analyze all data obtained from this proposal period.*

Name: *Stephanie Moore-Lotridge*
Project Role: *Post-doctoral Fellow*
Researcher Identifier (e.g. ORCID ID): 0000-0002-3045-4199
Nearest person month worked: *3*
Contribution to Project: *Dr. Moore-Lotridge conducted the proposed experiments to produce the reported data on the efficacy of a2AP ASO administration at the time of injury for preventing muscle calcification.*

Name: *John C. Reese*
Project Role: *Research Assistant*
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: *1*
Contribution to Project: Mr. Reese is responsible for mouse colony maintenance, laboratory management, and ordering of products needed for experiments.

Name: *Zachary Backstrom*
Project Role: *Research Assistant*
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: *2*
Contribution to Project: Mr. Reese is responsible for mouse colony maintenance, laboratory management, and ordering of products needed for experiments.

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?
Organization Name: Masonic Medical Research Institute (Dr. Jason McCarthy)
Location of Organization: Utica, NY
Partner's contribution to the project: Production of fibrin imaging agents for use in our animal models

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: Submitted