AWARD NUMBER: W81XWH-21-1-0870

TITLE: Acute to Chronic Pain Signatures in Traumatic Injury

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CONTRACTING ORGANIZATION: Pennsylvania State University, Hershey, PA

REPORT DATE: October 2022

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2022	Annual	01Sep 2021 - 31 Aug 2022

4. TITLE AND SUBTITLE

Acute to Chronic Pain Signatures in Traumatic Injury

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-21-1-0870

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Persistent and chronic pain are significant contributors to diminished quality of life following acute musculoskeletal injury. The goal of this project is to identify critical biomarkers to predict susceptibility/resilience to the development of chronic pain after a traumatic injury. Here, we are using a population of patients with blunt chest trauma with multiple (>2) closed rib fractures, as our published prospective data indicate the chronification of pain after multiple rib fractures observed in our institution ranges from 40 to 50%. Biomarkers assessed include 1) prognostic clinical factors that predict a predisposition for susceptibility and/or resilience to pain chronification; 2) functional brain imaging biomarkers associated with the development of chronic pain; and 3) nociceptive genetic patterns at the time of injury that are predictive of pain chronification.

15. SUBJECT TERMS

Pain; Trauma; Biomarkers

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	17	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Persistent and chronic pain are significant contributors to diminished quality of life following acute musculoskeletal injury. The goal of this project is to investigate chronification of acute pain in patients with blunt chest trauma with multiple (>2) closed rib fractures by assessing psychological, biological, and functional neural connectivity biomarkers during the transition from acute to chronic pain. Rib fractures are commonly recognized as a significant source of acute pain following injury; however, they also have a high rate of transition to chronic pain. Our published prospective data indicate the chronification of pain after multiple rib fractures observed in our institution ranges from 40 to 50%. There remains a large gap in understanding of how acute pain transitions to chronic pain and how clinical measures can predict pain chronification. The objective of this study is to identify critical biomarkers to predict susceptibility/resilience to the development of chronic pain using blunt chest trauma with multiple rib fractures as a model. As such, we intend to 1) identify prognostic clinical factors that predict a predisposition for susceptibility and/or resilience to pain chronification; 2) identify functional brain imaging biomarkers associated with the development of chronic pain; and 3) identify nociceptive genetic patterns at the time of injury that are predictive of pain chronification.

2. KEYWORDS:

Chronic Pain; Acute Pain; Trauma; Chronification

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Statement of Work (items in **blue** are either complete or currently ongoing)

Task	Time	Proposed/Actual Dates	
Major Task 1: Study Startup and Regulatory Approval	**Months**	**Proposed**	**Actual**
Subtask 1: Compose and submit protocol for IRB approval	1	9/30/2021	8/4/2021
Subtask 2: Submit and obtain HRPO approval	1	9/30/2021	9/28/2021
Subtask 3: Develop Manual of Operations for study team	2-3	11/30/2021	10/28/2021
Subtask 4: Develop REDCap database and data entry parameters	2-3	11/30/2021	10/20/2021
Milestone(s) Achieved: IRB/HRPO-approved protocol	3	11/30/2021	9/28/2021

Statement of Work Continued

Specific Aim 1: Identify prognostic clinical factors that predict a predisposition for susceptibility and/or resilience to pain chronification.

Task	Time	Proposed/Actual Dates	
Major Task 2: Identify clinical indicators that predict chronic pain in patients with multiple rib fractures	**Months**	**Proposed**	**Actual**
Subtask 1: Participant screening for eligibility	3-18	2/28/2023	Ongoing
Subtask 2: Informed consent and enrollment of ~150 pts	3-18	2/28/2023	13.3% Complete
Subtask 3: Extraction of patient records from EMR	3-18	2/28/2023	16.7% Complete
Subtask 4: Pain assessments and QST	3-18	2/28/2023	16.7% Complete
Subtask 5: Submit manuscript on clinical indicators of chronic pain	24	8/31/2023	NA
Milestone(s) Achieved: Baseline pain characteristics, determination of clinical predictors of chronic pain	24	2/28/2023	NA

Task	Time	Proposed/Actual Dates	
Major Task 3: Complete follow-up assessments and identify psychological factors that predict chronic pain	**Months**	**Proposed**	**Actual**
Subtask 1: 3-month follow-up assessments	6-21	5/31/2023	10.8% Complete
Subtask 2: 6-month follow-up assessments	9-24	8/31/2023	4.2% Complete
Subtask 3: Verification of chronic pain	9-24	8/31/2023	4.2% Complete
Subtask 4: Analysis/interpretation of psychological assessments	7-24	8/31/2023	4.2% Complete
Subtask 5: Submit manuscript on psych indicators of chronic pain	24	8/31/2023	NA
Milestone(s) Achieved: Determination of chronic pain outcomes, psychological predictors of chronic pain	24	2/28/2023	NA

Specific Aim 2: Identify functional brain imaging biomarkers associated with development of chronic pain.

Task	Time	Proposed/Actual Dates	
Major Task 4: Identify differences in functional connectivity that predict chronic pain	**Months**	**Proposed**	**Actual**
Subtask 1: Development of fMRI algorithms and protocol	1	9/30/3021	10/12/2021
Subtask 2: Completing fMRI scans at enrollment	3-18	2/28/2023	16.7% Complete
Subtask 3: Cleaning of images	4-20	4/30/2023	10% Complete
Subtask 4: Analysis and interpretation of data	18-24	8/31/2023	NA
Subtask 5: Statistical analysis of patient outcomes (from Aim 1) compared between chronic pain and non-chronic pain participants	22-24	8/31/2023	NA
Subtask 6: Submit manuscript on fMRI predictors of chronic pain	24	8/31/2023	NA
Milestone(s) Achieved: fMRI assessments for all patients and the time of injury, association of connectivity with pain outcomes, functional biomarkers of pain chronification	24	8/31/2023	NA

Specific Aim 3: Identify nociceptive genetic pattern at the time of injury that are predictive of pain chronification.

Task	Time	Proposed/Actual Dates	
Major Task 5: (For each major task, define the key hypothesis or the main study(s) to be tested.)	**Months**	**Proposed**	**Actual**
Subtask 1: Blood collection at enrollment	3-18	2/28/2023	15% Complete
Subtask 2: Sample processing and storage	3-22	6/30/2023	15% Complete
Subtask 3: Sample analysis	16, 24	12/31/2022, 8/31/2023	NA NA
Subtask 4: Statistical analysis of patient outcomes (from Aim 1) compared between chronic pain and non-chronic pain participants	22-24	8/31/2023	NA
Subtask 5: Submit comprehensive manuscript on combined findings	24	8/31/2023	NA
Milestone(s) Achieved: Genomic analysis for all patients that completed all 3 assessments and the time of injury	24	8/31/2023	NA

What was accomplished under these goals?

1) Major Activities: Major activities during this reporting period include the development of the study protocol, attainment of IRB and HRPO approval, development of a manual of operations, and development of the REDCap database to collect data. Additionally, enrollment was initiated during the current reporting period with the first participant enrolled on 12/17/2021. We currently have 20 participants enrolled with no loss to follow-up at this time.

2) Specific Objectives: The specific objectives during this period were study startup and initiation of participant enrollment. Both objectives were achieved within the proposed time period.

3) Significant Results or Key Outcomes: Nothing to report.

4) Other Achievements: Training of the study team on all procedures was accomplished during this reporting period.

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?

Our goals and objectives over the next reporting period include ramping up recruitment activities and continuing data collection and subject enrollment. Enrollment was stifled in the beginning as a result of COVID-related restrictions, however, going into the summer months with the University restrictions somewhat relaxed, we have been able to increase recruitment.

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

To boost recruitment, we made modifications to the study including sending invitation letters to potential participants that were discharged before a study team member could discuss the study with them. We also expanded the window for the first study visit to allow us to schedule the study visit to coincide with return medical appointments, which greatly increased participants' likelihood to participate in the study.

Actual or anticipated problems or delays and actions or plans to resolve them

Obtaining approval to conduct in-person research during the COVID-19 pandemic. In an effort to limit the exposure to COVID-19, the Pennsylvania State University organized the Penn State COVID Safety Committee which was tasked with reviewing and assessing the safety of every in-person human subjects study. After receiving IRB and HRPO approval, the protocol and additional safety SOPs had to be submitted to this committee and approved prior to the initiation of any in-person human subjects studies. This delayed the start of enrollment by a month and once the SOPs finally were approved, we were only approved to recruit fully vaccinated participants. Only being able to recruit fully vaccinated participants complicated enrollment as there is a large proportion of our population of interest that are unvaccinated (approximately 65% were unvaccinated or not fully vaccinated). We appealed to the COVID Safety Committee several times and finally received approval to recruit both vaccinated and unvaccinated participants a month later on 12/7/2021.

Unanticipated University closures and suspension of all in-person human subjects research due to the COVID-19 pandemic. Our first two participants were scheduled on 12/9/2021 and 12/14/2021. On 12/17/2021, the Penn State College of Medicine closed to observe the Pennsylvania State University winter break for the first time in the College's history. As such, the MRI facilities we needed to enroll participants were not available for research during the break that extended until 1/3/2022. Accordingly, our study had to pause recruitment during this time. Unfortunately, once winter break had commenced, the COVID epidemic had surged again, and the College of Medicine suspended all in-person human subjects research until 2/10/2022. Therefore, we were not able to recruit participants from 12/17/2021 to 2/10/2022. While this may have delayed enrollment, it has not had a significant effect on expenditures.

At the current time point, we predicted to have 102 participants enrolled; however, this was not possible partially due to the delays and additional requirements caused by the COVID-19 pandemic. As a result of health system changes, willingness to participate in research, and even patient flow in response to the pandemic, recruitment has been slower than originally anticipated. That said, study startup was completed earlier than predicted and we have had better retention than previously anticipated. We credit our highly engaged study team for the exceptional retention. The physician team members are involved in the care of all trauma patients, so they are able to build rapport and introduce the potential participants to our study nurse. Our chargeback RN has a fantastic bedside manner and takes the time while participants are still inpatient to introduce the study and answer any questions. She also follows up by phone to remind the potential participants of upcoming appointments and checks on the participant after undergoing the fMRI. Prior to the follow-up assessments, she reaches out to remind the participants and makes sure they receive the survey without problems. This repeated interaction has ensured that participants are engaged in the study and we have thus far had total compliance. Because the participants have to schedule a return visit for their fMRI, we have been scheduling their study visit appointments to coincide with scheduled medical visits. This also has proven to be effective in preventing no-shows, which are common with MRI studies. Because of the tremendous retention we have maintained, we predict that our target enrollment is lower than initially predicted.

In the next reporting period, our main focus will be recruitment and enrollment. The COVID-19 pandemic is not yet behind us, which means that additional closures and adjustments may be required to keep participants and study team members safe. Currently, restrictions have been lifted and we are able to recruit participants without any further obstacles. The Hershey Medical Center had the highest rate of trauma admissions in the region in 2021 and we are confident that we will maintain sufficient recruitment to meet our goals.

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

Significant changes in use or care of human subjects

PROTOCOL (1 of 1 total):

Protocol [HRPO Assigned Number]: E024482.1a

Title: Acute to Chronic Pain Signatures in Traumatic Injury

Target required for clinical significance: 120

Target approved for clinical significance: 150

SUBMITTED TO AND APPROVED BY:

- Protocol, Informed Consent Form, Data Plan submitted to the Pennsylvania State University College of Medicine Institutional Review Board 7/1/2021, Approved 8/4/2021
- Protocol, Informed Consent Form, and HRPO Protocol Submission Form submitted to the USAMRDC DoD Human Research Protection Office (HRPO) 8/5/2021, Approved 9/28/2021
- Protocol, COVID-19-specific SOPs submitted to the Pennsylvania State University COVID Safety Committee 9/29/2021, Approved for vaccinated participants only 10/28/2021
- Protocol, COVID-19-specific SOPs resubmitted to the Pennsylvania State University COVID Safety Committee 11/22/2021, Approved for vaccinated and unvaccinated participants 12/7/2021

STATUS:

(i) Number of subjects recruited/original planned target: 21/150
Number of subjects screened/original planned target: 151/no target for screening
Number of patients enrolled/original planned target: 20/150
Number of patients completed/original planned target: Initial visit 20/120; 3-Month Follow-up 13/120; 6-Month Follow-Up 5/120

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:

- Modification #1 was submitted to the Penn State IRB and approved on 10/11/2021. The protocol and consent form were modified slightly to clarify procedures related to sensory testing and the timing of the study visit. We also modified both the protocol and consent form to include reimbursement for travel expenses. These changes were approved on an expedited basis and determined to be non-significant changes that did not increase risk to the participants nor change the direction of the project.
- Modification #2 was created on 10/19/2021 but then discarded prior to review. No actual changes were made.
- The original Modification #1 submission used an incorrect version of the original documents and therefore, Modification #3 was a resubmission of Modification 1 using the correct version of the original documents. This was submitted on 10/1/2021 and approved on 10/21/2021. No actual changes were made to the protocol or consent form.

- Modification #4 was submitted to the Penn State IRB on 11/30/2021 and approved on 11/30/2021. This modification added an invitation letter to send to potential participants if they are discharged before a member of the study team is able to meet with them to explain the study. Additionally, we included a phone script for contacting potential participants who have responded to the invitation letter and indicated an interest in learning more about the study. This modification also added the study to the "Study Finder" database so that if a potential participant receives an invitation letter, they can look at the study online before deciding if they would like to be contacted by a study team member. This modification also made a correction to the blood collection tube description. We will be using 7 ml lavender top tubes, not 4 ml red top tubes (however, we left the color of the tube out as it is not relevant information). These changes were approved on an expedited basis and determined to be non-significant changes that did not increase risk to the participants nor change the direction of the project.
- Modification #5 was submitted to the Penn State IRB on 12/16/2021 and approved on 12/17/2021. This modification expanded the time for scheduling of the first study visit. Originally, the protocol stated that we would try to schedule the visit within 3-7 days of discharge or at the time of a follow-up appointment, but because the timing relative to discharge is not of importance to the study, we simplified the language to state that we will schedule the visit as close to discharge as possible rather than give an estimated range of days.
- Modification #6 was submitted to the Penn State IRB on 7/21/2022 and approved on 8/5/2022. The purpose of this modification was to add additional study personnel. These personnel include Corinne Augusto, a second year neuroscience doctoral student who will participate in data collection and Cheryl Blaha, RN, as a backup charge nurse should the current study nurse be unavailable due to illness or PTO.
- Modification #7 was submitted to the Penn State IRB on 7/21/2022 and approved on 7/21/2022. This modification included changes to the protocol and informed consent form to update the travel reimbursement rate to align with the new reimbursement rate of $0.625 per mile. Travel reimbursement is offered to participants that visit campus for their study visit at a time that is not coordinated with a clinical visit.

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

There were no adverse events/unanticipated problems involving risks to subjects or others during this reporting period.

Significant changes in use or care of vertebrate animals

No animal use research has been proposed to complete the Statement of Work.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

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

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?

Name:	Jennifer Nyland
Project Role:	PD/PI
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-4549-3617
Nearest person month worked:	4.8
Contribution to Project:	Dr. Nyland is the PD/PI of this project and has been responsible for study design, regulatory approval, and overseeing all procedures and data collection.
Name:	Aimee Cauffman
Project Role:	Research Nurse/Study Coordinator
Researcher Identifier (e.g. ORCID ID):	Scopus ID: 56764625100
Nearest person month worked:	2.4
Contribution to Project:	Ms. Cauffman is a research nurse and serves as the coordinator of this study. She has been responsible for screening, consent, sensory testing, and blood draws.
Name:	Sara Mills-Huffnagle
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-6722-2586
Nearest person month worked:	1.8
Contribution to Project:	Ms. Mills-Huffnagle is a graduate student in the Nyland lab who has performed work on the REDCap database and participated in data collection.
Name:	Prasanna Karunanayaka
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-1558-8981
Nearest person month worked:	1.8
Contribution to Project:	Dr. Karunanayaka has been responsible for the development of fMRI protocols and overseeing fMRI data collection.
Name:	Piotr Janicki
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	Scopus ID: 7004816132
Nearest person month worked:	2.4
Contribution to Project:	Dr. Janicki has been responsible for developing the sensory testing protocols, teaching study team members on the use of the equipment and helping to screen for potential participants.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Jennifer Nyland

Pending grants now active:

Title: Immune and Neuroendocrine Mediators of Sex-Differences in Pain Following Traumatic Burn Injury
PD/PI: Nyland
Time Commitments: 5.2 calendar months
Supporting Agency: NIH/NIGMS R35 GM146774
Scientific Overlap: None

Title: Use of Micro-Doppler Radar to Identify Service Members at Risk for Musculoskeletal Injury: A Gold Standard Comparison
PD/PI: Onks
Time Commitments: 1.2 calendar months **Role: Co-I**
Supporting Agency: CDMRP/PRORP W81XWH-22-1-0684
Scientific Overlap: None

Active grants now closed:

Title: Use of a GLP-1 Agonist to Treat Opioid Use Disorder in Rats and Man
PD/PI: Grigson and Bunce
Time Commitments: 3.6 calendar months **Role: Co-I**
Supporting Agency: NIH/NIDA, 1UG3DA050325-02

Title: Use of a GLP-1 Agonist to Treat Opioid Use Disorder in Rats and Man
PD/PI: Grigson
Time Commitments: 0.36 calendar months **Role: Co-I**
Supporting Agency: NIH/NIDA, 1UG3DA050325-02S2

Title: Applied Research Consortium of Hershey (ARCH): Catalyzing Meaningful Collaborations in Pain and Substance Use Research
PD/PI: Nyland
Time Commitments: 1.2 calendar months
Supporting Agency: Penn State College of Medicine (No number)

Aimee Cauffman
Nothing to report.

Piotr Janicki
Nothing to report.

Prasanna Karunanayaka

Pending grants now active:

Title: Linking Olfactory Deficits to Memory Impairment and AD Neurodegeneration
PD/PI: Karunanayaka
Time Commitments: 3 calendar months
Supporting Agency: NIH/NIA R01 AG070088
Scientific Overlap: None

Sara Mills-Huffnagle

Pending grants now active:

Title: Intrathecal Administration of the Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist in Pregnant Rats
PD/PI: Mills-Huffnagle
Time Commitments: NA
Supporting Agency: NIH/NCATS TL1TR002016
As of August 1, 2022, Ms. Mills-Huffnagle will no longer be supported on this project, as she has been awarded a TL1 fellowship through NIH/NCATS to support an independent project.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: