AWARD NUMBER: W81XWH-22-1-0473

TITLE: Using Big Data and Machine Learning Approaches to Discover Prognostic Biomarkers and Drugs for Neuropathic Pain in Chronic SCI

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CONTRACTING ORGANIZATION: University of California San Francisco

REPORT DATE: AUGUST 2023

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
AUGUST 2023	Annual	15 Jul 2022 – 14 Jul 2023

4. TITLE AND SUBTITLE

Using Big Data and Machine Learning Approaches to Discover Prognostic Biomarkers and Drugs for Neuropathic Pain in Chronic SCI

5a. CONTRACT NUMBER
W81XWH-22-1-0473

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S) Dr. Nikolaos Kyritsis, Ph.D

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

University of California San Francisco - Medical Center 3333 California Street, San Francisco, CA 94143

8. PERFORMING ORGANIZATION REPORT NUMBER

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
Chronic neuropathic pain ranks among the top three secondary complications that significantly impact the lives of individuals following spinal cord injuries (SCIs). It is estimated that 50% to 80% of SCI patients will experience neuropathic pain within six months of their injury, and as of now, there exists no effective treatment. Research has consistently shown that early and preemptive interventions are the most successful means of alleviating pain symptoms. Consequently, the development of predictive models capable of forecasting neuropathic pain months in advance could provide clinicians with a valuable tool to address this critical medical complication. In pursuit of this objective, our study aims to construct a predictive model using three distinct types of acute care data. By utilizing data from the TRACK-SCI database, we have identified all SCI patients for whom we possess chronic neuropathic pain status information. We have been collecting and analyzing the following data points: 1) acute care clinical variables, 2) gene expression levels from white blood cells obtained within 24 hours of the injury, and 3) routinely collected blood analytes for the entire duration of their hospital stay. We are currently employing machine learning algorithms to utilize the aforementioned acute care data in order to develop mathematical models that can estimate the probability of an SCI patient developing neuropathic pain between six and twelve months after their injury.

15. SUBJECT TERMS
Spinal cord injury, neuropathic pain, machine learning, predictive models.

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
U	U	U	UU	11	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

INTRODUCTION

A spinal cord injury (SCI) is a devastating condition that, as of now, lacks any available treatment. It affects millions of people worldwide, significantly diminishing their quality of life and life expectancy. In addition to the obvious motor and sensory impairments, SCIs lead to numerous secondary medical complications, including neuropathic pain, sexual dysfunction, bladder and bowel problems, and autonomic dysreflexia, among others. The prevalence of neuropathic pain in SCI patients ranges from 50% to 80% within the first year after the injury and consistently ranks as one of the top three symptoms that severely hinder their quality of life. Despite recent advancements in our understanding of pain mechanisms, an effective and dependable treatment regimen for neuropathic pain following SCI remains elusive.

The efficacy of various treatment approaches varies significantly, often accompanied by substantial side effects, with the most critical concern being the risk of opioid addiction. Recent reports suggest that early diagnosis of neuropathic pain is the most effective "treatment" since neuropathic pain symptoms can become unmanageable if not addressed promptly. Therefore, the discovery of biomarkers for predicting neuropathic pain development and the development of non-opioid medications are the most pressing research priorities in the field of SCI and neuropathic pain.

Our proposal encompasses two primary objectives. Firstly, we aim to create a prognostic model for predicting the development of neuropathic pain at 6 and/or 12 months following an SCI, utilizing data collected during the acute phase of hospitalization after the injury. Secondly, we intend to identify systemic gene expression patterns in the white blood cells (WBC) of chronic SCI patients that are prevalent in those experiencing neuropathic pain. We will then use these patterns to computationally predict and validate in vitro the effectiveness of known non-opioid compounds that target these patterns.

KEYWORDS

Spinal cord injury, neuropathic pain, machine learning, predictive models, drug screening

ACCOMPLISHMENTS

What were the major goals of the project?

Per the approved Statement of Work (SoW) the goals that would be completed during the first 12 months of the funding period were:

Description of Aim or Task	Timeline (months)	Site 1 (UCSF)	Site 2 (UBC)
Major Task 1: Submit regulatory documents and obtain necessary approvals for study initiation	**1-6**	NK	
Subtask 1.1: Amend the TRACK-SCI IRB to include acquiring a second blood sample at the chronic stage of SCI for the *in vitro* experiment of Aim 3.	**1-2**	NK	
Subtask 1.2: Obtain secondary use approval to analyze human WBC transcript data sets at UCSF IRB.	**1-2**	NK	
Subtask 1.3: Submit documents for this secondary use of the human WBC RNA-seq datasets and biospecimen to HRPO.	**2-4**	NK	
Subtask 1.4: Review and modify regulatory documents and obtain HRPO approval.	**4-6**	NK	
Milestone(s) Achieved: TRACK-SCI IRB amended; UCSF *IRB approval obtained; HRPO approval received.*			

Per the SoW the goals that would be initiated during the first 12 months of the funding period but would be completed during the 2nd and 3rd year are:

Specific Aim 1: Discover prognostic biomarkers for the development of NP after traumatic SCI in human patients			
Major Task 2: Update and validate the current predictive model for neuropathic pain using acute care variables.	7-36	NK/MB/JC/ AF/RH	KK
Subtask 2.1: Using the constantly growing TRACK-SCI database, we will add new patients' data to re-train and validate the model. We will use data only from ZSFG patients at this step (expected enrollments = 60-75 patients, 25-35 with follow-up data).	7-36	NK/MB/JC/ AF/RH	KK
Subtask 2.2: Use TRACK-SCI data collected at the other affiliate sites (UCSF Fresno, OSU, UW) to validate the final predictive model generated in Subtask 2.1. (expected patients in the validation cohort across all sites = 20-30).	31-36	NK/AF/RH	KK
Major Task 3: Use acute WBC transcriptomic data to predict the development of neuropathic pain after SCI.	7-36	NK	-
Subtask 3.1: Analyze the raw WBC RNAseq data to generate a transcript count table. (expected patients: minimum 98, and up to 130 at the end of the 3rd year).	7-36	NK	-
Subtask 3.2: Perform differential gene expression analysis between the group of patients who develop neuropathic pain after SCI and those who do not.	7-36	NK	-
Subtask 3.3: Perform Weighted Gene Co-Expression Network Analysis and discover gene modules enriched in SCI patients who eventually develop neuropathic pain at 6- and/or 12-months after injury.	7-36	NK	-
Major Task 4: Use routinely collected blood analytes during the acute hospital stay to predict the development of neuropathic pain after SCI.	7-36	NK/MB/JC/ AF/RH	KK
Subtask 4.1: Collect, curate, and harmonize all the blood test data for all TRACK-SCI enrolled patients from the Academic Research Systems of UCSF (as of now, we have 459 unique blood tests for the first 135 SCI patients at ZSFG).	7-36	NK/MB/JC/ AF/RH	-
Subtask 4.2: Use machine learning methods such as XGBoost and URP-CTREE and automated machine learning platforms (partnering with DataRobot) to create a model predicting the development of neuropathic pain using only the blood test results.	7-36	NK/MB/JC/ AF/RH	KK
Milestone(s) Achieved: at least three different predictive models for neuropathic pain development; a research application to quickly make predictions upon new patient enrollment created; at least one manuscript presenting the predictive models; at least one conference presentation.			

What was accomplished under these goals?

During the initial 12 months of our funded research project, we achieved several significant milestones:

1. We successfully completed all the necessary regulatory documentation and obtained the required approvals.
2. In the ongoing TRACK-SCI study, we have continued to enroll SCI patients, rigorously screening them to ensure their eligibility for our study.
3. For the eligible patients identified, we have been actively gathering pertinent data essential for the development of our predictive models.
4. We have submitted our initial manuscript for publication, and it is presently undergoing review at the Annals of Neurology journal.

To provide specific details about our progress, at the inception of our study, TRACK-SCI had enrolled 135 patients at the Zuckerberg San Francisco General Hospital. Among these, we possessed chronic neuropathic pain data for 61 individuals. Subsequently, we have enrolled an additional 53 SCI patients within the TRACK-SCI program, resulting in neuropathic pain data for 12 of them. In summary, our dataset now comprises 73 SCI patients with chronic neuropathic pain data. Out of these 73 patients, 46 (63%) developed neuropathic pain between 6 and 12 months following their injury. Our initial projections suggested that over the entire funding period, we would accumulate data for 25-35 more patients with chronic neuropathic pain, and our progress during the first year places us on track to meet this goal.

Simultaneously, as we continue enrolling patients in TRACK-SCI, we are also actively extracting various data points for these 73 patients. This includes their acute care records, white blood cell RNAseq data, and routine blood analyte values. The acute care data are already stored within TRACK-SCI's RedCap database, and the WBC RNAseq data are readily available for the initial 61 SCI patients with neuropathic pain data. Furthermore, we have already extracted and meticulously curated the routine blood analyte data for the first 61 patients. Additionally, we have initiated a query to the UCSF Academic Research System for the extraction of data concerning the latest 12 eligible patients.

How were the results disseminated to communities of interest?

As mentioned before, our first manuscript is under review at the journal Annals of Neurology.

What do you plan to do during the next reporting period to accomplish the goals?

We will continue our ongoing screening of SCI enrollments and follow-up visits to identify eligible patients for our study. Concurrently, we will continue to extract their acute care data, WBC RNAseq, and routinely collected blood analytes. We have been diligently preparing scripts in the R coding language, which significantly accelerates the addition and curation of newly acquired data.

While our initial plan was to generate our predictive models during the final year of the funding period after enrolling the planned 25-35 new patients, it appears likely that we may reach this target a full year ahead of schedule. If this turns out to be the case, we will aim to initiate modeling toward the end of the upcoming reporting period, utilizing the patients enrolled during the final year for validation of our predictive models.

Finally, by the end of the next reporting period, we anticipate completing the RNAseq analysis. Through the Weighted Gene Co-Expression Network Analysis, we will identify eigengene modules associated with the development of chronic neuropathic pain. Subsequently, we will leverage these eigengene modules on the CMap platform to pinpoint non-opioid chemical compounds capable of reversing the expression of these

modules. The resulting list of predicted compounds will be utilized for in vitro screening during the project's final year.

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.

CHANGES/PROBLEMS

Nothing to report.

PRODUCTS

Publications, conference papers, and presentations

Fond K, Torres-Espin A, Chou A, Fernandez X, Moncivais S, Huie J, Hemmerle D, Keller A, Singh V, Pascual L, DiGiorgio A, Talbott J, Whetstone W, Pan J, Weinstein P, Dhall S, Ferguson A, Bresnahan J, Beattie M, Kyritsis N. Assessing and predicting neuropathic pain after spinal cord injury: a TRACK-SCI study. Under review (Annals of Neurology).

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.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Nikolaos Kyritsis*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-7801-5796*
Nearest person month worked:	5
Contribution to Project:	*Dr. Kyritsis has been involved in every aspect of the study and oversees the entire project.*
Funding Support:	

Name:	*Kenneth Fond*
Project Role:	*Staff Research Associate*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-9154-6599*
Nearest person month worked:	1
Contribution to Project:	*Mr. Fond was involved in the analysis of the acute care clinical variables of the first 61 eligible patients*
Funding Support:	

Name:	*Mayra Arellano*
Project Role:	*Staff Research Associate*

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	*Ms. Arellano is involved in the screening of TRACK-SCI study for eligible patients and in the extraction of their relevant acute data*
Funding Support:	

Name:	*John Russell Huie*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-5594-4277*
Nearest person month worked:	1
Contribution to Project:	*Dr. Huie has been involved in the generation of R scripts that will streamline the addition of newly acquired patient data to our dataset.*
Funding Support:	

Name:	*Adam Ferguson*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-7102-1608*
Nearest person month worked:	1
Contribution to Project:	*Dr. Ferguson is the director of Data Science and is providing his guidance in the data curation before we begin the machine learning modeling.*
Funding Support:	

Name:	*Michael Beattie*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-9463-3631*
Nearest person month worked:	1
Contribution to Project:	*Dr. Beattie is the Director of TRACK-SCI and ensures the smooth transfer of data from TRACK-SCI to our study. He and the PI meet weekly for updates on the project.*
Funding Support:	

Name:	*Jacqueline Bresnahan*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0003-2243-7054*
Nearest person month worked:	1
Contribution to Project:	*Dr. Bresnahan along with Dr. Beattie provides critical consultation on all aspects of the project.*
Funding Support:	

Name:	*John Kramer*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1

Contribution to Project:	*Dr. Kramer and the PI meet quarterly to discuss the project updates and provide his expertise and guidance to the proper data management for analysis.*
Funding Support:	

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?

Dr. Kramer is an associate professor at University of British Columbia, in Vancouver, Canada.