

AWARD NUMBER: W81XWH-20-1-0245

TITLE: Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI)

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REPORT DATE: August 2023

TYPE OF REPORT: Annual

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

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REPORT DOCUMENTATION PAGE

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OMB No. 0704-0188

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1. REPORT DATE August 2023			2. REPORT TYPE Annual		3. DATES COVERED 01Aug2022-31Jul2023	
4. TITLE AND SUBTITLE Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI)					5a. CONTRACT NUMBER W81XWH-20-1-0245	
					5b. GRANT NUMBER SC190233	
					5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Michael S. Beattie, Jacqueline Bresnahan, Xuan Duong Fernandez E-Mail: Michael.beattie@ucsf.edu ; xuan.duongfernandez@ucsf.edu					5d. PROJECT NUMBER	
					5e. TASK NUMBER	
					5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Regents of the University of California, San Francisco 1855 Folsom St. STE 425 San Francisco, CA 94103					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 Acute spinal cord injury (SCI) in both the military and civilian settings requires a variety of immediate emergency critical care decisions to stabilize the patient, evaluate the level and severity of injury, whether, when, and how to realign & stabilize the spine based radiological findings, especially MRI. Protocols for critical care in the intensive care unit (ICU) can include pain control, respiratory support, cardiovascular management, bowel/bladder care, early physical and occupational therapies, and psychological support. A huge team of health care professionals is required and decisions must be coordinated across multiple departments and units. Although there are established standards of care for acute SCI, these vary across trauma centers, and there are in fact very few evidence-based studies of SCI critical care to provide solid guidance for the many treatment decisions facing the team. In short, even the best teams don't know what the best practices are. <i>Our objective is to provide a comprehensive prospective analysis of multiple variables in acute SCI that impact long-term outcomes.</i>						
15. SUBJECT TERMS Spinal cord injury; prospective clinical trial						
16. SECURITY CLASSIFICATION OF:				17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 7	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified	19b. TELEPHONE NUMBER (include area code)			

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1. Introduction

History of TRACK-SCI. This is an expansion award linked to SC150198. SC150198 supported a prospective observational study of acute SCI, enrolling patients at two different UCSF level 1 trauma centers: The UCSF/ Zuckerberg San Francisco General Hospital and Trauma Center (UCSF/ZSFG), located in San Francisco, and the UCSF Fresno Medical Center in Fresno, CA. The two sites are administratively linked, but have separate, hospital-based IRBs. During the SC150198 award period, we developed data collection strategies based on prior retrospective studies supported in part by a prior SCIRP award (SC120259), and solidified our team of analytic and clinical research personnel. The expansion award supports continued enrollment at these centers, and provides funding to add and support an additional site at The Ohio State University Wexner Medical Center located on the OSU campus in Columbus, OH.

Study Objective: Our overarching hypothesis is based on the premise that the spinal cord is especially vulnerable to secondary injury in the first hours and days following injury, and that secondary injury can be minimized by identifying and optimizing the early critical care variables that are most important in determining recovery. Our secondary hypothesis is that white blood cells (WBCs) act as 'sentinels' encoding critical biological information related to injury severity, repair, and long-term recovery after SCI, and that we can query this information to provide SCI-induced gene expression patterns that can serve as biological indicators of injury severity and prognosis, and that could be validated to provide useful biomarkers for diagnosis, prognosis, and treatment. The long-term goal is to use these data, along with sophisticated data analytics provided by the UCSF Brain and Spinal Injury Center (BASIC) bioinformatics team (led by Dr. Adam Ferguson) to provide acute care predictors of outcomes at 6 months and 1 year that can be used to optimize treatments of acute SCI.

2. Keywords. Spinal cord injury, prospective observational study, critical care variables, magnetic resonance imaging (MRI), white blood cells, transcriptomics

3. Accomplishments

The last yearly progress report was submitted August 30, 2022. Since then, TRACK-SCI has:

- Enrolled 30 additional participants at UCSF/ZSFG and 7 at Ohio State University Medical Center (OSU) for a total of 255 overall (UCSF=178, UCSF Fresno=62, OSU=15).
- Additional enrollment NOT FUNDED by SC190233 include 1 from University of Washington (no longer enrolling patients), and 11 from the University of Utah Medical Center. The Utah site is new and funded at a low level (<\$40K) by an NCE of the Crain H. Neilsen Foundation special project award (Beattie, PI).
- OSU funding ended on July 31, 2023, i.e. their subcontract was not extended with the current NCE).
- UCSF Fresno stopped enrollment after year 2 as reported in the YR2 progress report.
- University of Utah Medical Center (Not supported by SC190233) obtained IRB approvals, training of CRCs, and the addition of PI Ramesh Grandhi, MD who is in Neurosurgery. The team there has also engaged the PM&R team at the Craig H. Neilsen Rehabilitation Hospital to help with follow up evaluations and ISNCSCI exams. Enrollment has begun (with 7 participants to date) as reported above.
- TRACK-SCI has continued to involve UCSF medical students, post-docs, residents, and fellows in data collection and analysis. The executive committee established a more stringent process for approving projects using TRACK-SCI data for UCSF/ZSFG, which requires that a member of the bioinformatics team associated with TRACK-SCI be assigned to each project. This is intended both as a data curation/analysis quality control, and as a means of providing in-process training on statistical treatment of clinical data for trainees. Progress towards ensuring continuing productivity of TRACK-SCI: Funding for TRACK-SCI continues via an NCE for

SC190233 that extends to July 31, 2024, and an NCE for the Craig H. Neilsen special project award (M. Beattie, PI) that extends to August 31, 2024. Some funds from other awards are also supporting Dr. Nikos Kyritsis, with minor contributions of our TRACK-SCI CRC salaries (W81XWH2110505, "Leveraging clinical transcriptomic data for targeted drug interventions in preclinical models of SCI" and W81XWH2210473, "Using Big-Data and Machine Learning Approaches to Discover Prognostic Biomarkers and Drugs for Neuropathic Pain in Chronic SCI", Nikos Kyritsis, Ph.D., PI, total awards ~\$1.6M). Applications submitted to the NINDS biomarker discovery program (R61/33) and the DoD CDMRP SCIRP program (2 from Dr. Rajiv Saigal) were not funded. An NIH R01 submitted by Dr. Kyritsis aimed at expanding the blood transcriptomics data collection and analysis for TRACK-SCI was recently reviewed, and while not funded, it received a score and reviewer comments that support a resubmission, which will be submitted Nov 5, 2023.

4. IMPACT

TRACK-SCI continues to have impact, as noted by our clinical colleagues at national meetings who report interest in TRACK-SCI findings, which have been reported at the Congress of Neurological Surgeons, and American Association of Neurological Surgeons meetings this last year. Locally, the neurosurgical service at ZSFG/UCSF continues to move forward with efforts to reduce time to surgery for SCI patients, and to control blood pressure and spinal cord perfusion pressure (SCPP) by monitoring both mean arterial pressure and intrathecal pressure measured at a lumbar drain.

TRACK-SCI also provides baseline data collection and shares CRC and personnel costs with the CAMPER study of intraspinal pressure and outcomes, and two new clinical studies being initiated at ZSFG/UCSF (an anti-body sponsored by Mitsubishi and the "IN-TWIN" (Incomplete cervical SCI without instability, sponsored by the AO Foundation/AO Spine. All participants on those studies are also enrolled in TRACK-SCI, under separate consent.

Importantly, the TRACK-SCI team has remained mostly intact with members of the clinical research team from all departments continuing to attend weekly data and research meetings, and these are now being held as hybrid Zoom/on site meetings located in the new conference rooms at Pride Hall on the ZSFG campus. Further impact is shown by our continuing discussions with the Praxis SCI Institute, and with Dr. Brian Kwon, concerning an international collaboration that will leverage the Rick Hansen registry data and TRACK-SCI dataset structure to provide data harmonization and possible expansion of TRACK-SCI data collection to Canada in addition to our slow but sure addition of sites in the US.

5. CHANGES/PROBLEMS

1. This past year saw a significant increase in patient enrollment at USCF/ZSFG, coincident with the reduced level of COVID-19 infections and the lifting of clinical research restrictions.

2. The Brain and Spinal Injury Center moved from its home in Building 1 at the ZSFG campus (built in 1919, and not in compliance with University of California earthquake and disaster codes) to a brand new building on the ZSFG campus, Pride Hall. The new facility provides for an integrated research and academic environment for all UCSF faculty and researchers located on the ZSFG campus, and includes a low touch clinical research center, organized under the UCSF CCRC, that will provide much better facility for 6 and 12 month return visits for TRACK-SCI participants. Faculty Clinical researcher coordinators for both TRACK-SCI and TRACK-TBI (G.T. Manley, PI) have workstations and offices located on the third and fourth floors, in dry lab space that is adjacent to the wet-lab facilities used by the BASIC preclinical SCI and TBI teams. In addition, the space fosters collaboration with other major research enterprises at ZSFG including the department of Orthopedics, the Division of Experimental Medicine Immunology group, and the Center for Cerebrovascular Research. BASIC and TRACK-SCI investigators have active collaborations with these groups. The clinical research center also has dedicated freezer space for the TRACK-SCI (and TRACK-TBI) biospecimen storage needs. The new facilities are expected to greatly enhance the experiences of both TRACK-SCI researchers and participants. Hooray.

3. The future of TRACK-SCI looks bright, but will be dependent upon continued federal and/or private foundation funding. The current PI, Dr. Beattie, is in the process of reducing commitment to active research, and has retired from the full-time faculty, retaining a 43% University of California "recall" position which is concentrated on transitioning TRACK-SCI to new leadership and providing advice and help for the center's

younger faculty and researchers. Dr. Jacqueline Bresnahan, who has helped lead the group along with Dr. Beattie, is in a similar position. New leaders include Dr. Nikos Kyrtsis, who has already established his lab and ties to the TRACK-SCI clinical research effort through 2 DoD grants (with more NOH and DoD applications pending), Dr. Adam Ferguson, who is now a full professor and leads the Bioinformatics group at BASIC, which is critical for TRACK-SCI data curation and analysis, Dr. Anthony DiGiorgio, who leads the spinal cord injury clinical team, and Dr. Rajiv Saigal, an M.D./Ph.D.-trained neurosurgeon and former UCSF resident who moved to UCSF recently from the University of Washington.

6. PRODUCTS

Publications for this award since the last annual PR:

1. Appendicular Fracture and Polytrauma Correlate with Outcome of Spinal Cord Injury: A Transforming Research and Clinical Knowledge in Spinal Cord Injury Study.

Miclaui TA, Torres-Espin A, Morshed S, Morioka K, Huie JR, El Naga AN, Chou A, Pascual L, Duong-Fernandez X, Kuo YH, Weinstein P, Dhall SS, Bresnahan JC, Beattie MS, DiGiorgio A, Ferguson AR; Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI) Investigators. J Neurotrauma. 2022 Aug;39(15-16):1030-1038. doi: 10.1089/neu.2021.0375. Epub 2022 Mar 25. PMID: 35255740

2. Hypotension requiring vasopressor treatment and increased cardiac complications in elderly spinal cord injury patients: a prospective TRACK-SCI registry study.

Agarwal N, Blitstein J, Lui A, Torres-Espin A, Vasnarungruengkul C, Burke J, Mummaneni PV, Dhall SS, Weinstein PR, Duong-Fernandez X, Chou A, Pan J, Singh V, Ferguson AR, Hemmerle DD, Kyrtsis N, Talbott JF, Whetstone WD, Bresnahan JC, Beattie MS, Manley GT, DiGiorgio A. J Neurosurg Spine. 2023 Mar 17:1-9. doi: 10.3171/2023.2.SPINE221043. Online ahead of print. PMID: 36933260

3. "Safety and Comparative Efficacy of Initiating Low Molecular Weight Heparin Within 24 Hours of Injury or Surgery for Venous Thromboembolism Prophylaxis in Spinal Cord Injury Patients: A Prospective TRACK-SCI Registry Study", Austin Lui, M.S.1, Christine Park, M.D.2, Timothy Chryssikos, M.D., Ph.D.2, Hannah Radabaugh, Ph.D.2, Arati Patel, M.D.2, Alexander Aabedi, M.D.2, Adam R. Ferguson, M.S., Ph.D.2,3,4,5, Abel Torres-Espin, Ph.D.2,3,4, Praveen V. Mummaneni, M.D., M.B.A.2,3,4, Sanjay S. Dhall, M.D.2,3,4, Xuan Duong-Fernandez, B.A.2,3,4, Rajiv Saigal M.D.8, Ph.D., Austin Chou, Ph.D.2,3,4, Jonathan Pan, M.D., Ph.D.1,9, Vineeta Singh, M.D.6, Debra D. Hemmerle, R.N., Ph.D.2,3,4, Nikos Kyrtsis, Ph.D.2,3,4, Jason F. Talbott, M.D., Ph.D.4,10, Lisa U. Pascual M.D.11, J Russell Huie Ph.D.2,3,4, William D. Whetstone, M.D.12, Jacqueline C. Bresnahan, Ph.D.2,3,4, Michael S. Beattie, Ph.D.2,3,4,5, Philip R. Weinstein M.D.2,6,13, Geoffrey T. Manley, M.D., Ph.D.2,14, Anthony DiGiorgio, D.O., M.H.A.2,3,4,1 – NEUROSURGICAL FOCUS-Oct-23-23-362R1. (in press).

7. Participants and other collaborating organizations.

- A. *Craig H. Neilsen Foundation support for TRACK-SCI:* Support for TRACK-SCI from the Neilsen Foundation is continuing under a no-cost extension of "a special project award entitled "Center of Spinal Cord Excellence", PI: M. Beattie, awarded from 09/30/2016-09/29/2021 with no-cost extension until 09/30/2023.
- B. *Other TRACK-SCI sites supported by CH Neilsen start-up grants*
 - a. University of Washington/Harbor Medical Center, Department of Neurological Surgery. PI: Hofstetter. (Discontinued, July 2023)
 - b. University of Utah School of Medicine, PI: Ramesh Grandhi.
- C. *Other sites under development as potential TRACK-SCI sites:*
 - a. University of Wisconsin College of Medicine, Milwaukee.
 - b. Duke University Medical Center, Durham
 - c. LSU Medical Center, New Orleans.

D. In addition, we are continuing the planning stages of a collaboration with the Praxis SCI Institute in Canada to provide TRACK-SCI data collection strategies and structure as an addition to the well-established Rick Hansen SCI registry, which collects data from multiple Canadian trauma centers, and with Dr. Brian Kwon at University of British Columbia/ICORD to add our RNA biomarker development program to the protein-based biomarker effort in his group. Along with the larger NIH applications noted above, this effort will help to disseminate and add to the TRACK-SCI effort to provide new strategies for diagnosis and treatment of acute SCI.