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

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CONTRACTING ORGANIZATION: University of California, San Francisco, CA

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b>  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><b>Our objective is to provide a comprehensive prospective analysis of multiple variables in acute SCI that impact long-term outcomes.</b></i>					
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# TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	5
5. Changes/Problems	5
6. Products	6
7. Participants & Other Collaborating Organizations	6

## 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, 2021. Since then, TRACK-SCI has:

- Enrolled 10 additional participants at UCSF/ZSFG and 7 at Ohio State University Medical Center (OSU) for a total of 218 overall (UCSF=148, UCSF Fresno=62, OSU=8).
- OSU is now covered by the UCSF central IRB, and the PI is Dr. Stephanus Viljoen, Department of Neurosurgery. The site is also now obtaining follow-up data from its on-campus rehabilitation hospital, and has successfully obtained and processed blood samples for the RNAseq biomarker project for 7 participants. While accrual is slow, the site is functioning well at this point. Funding for OSU is provided by this SC190233 TRACK-SCI expansion award.
- UCSF Fresno has not enrolled new participants since the departure of PI Dr. Kuo last year, although they have continued to work to add longer term follow-up data to the RedCap database. Due to changes in the structure of the neurosurgical service and the continued stress of COVID-related personnel issues, we do not expect this site to enroll any more participants.
- Finalized the addition of University of Washington Harbor View Medical Center, activating a start-up fund supported by a CH Neilsen award to provide salary for a CRC and the current PI, Dr. Hofstedter. The previous PI, Dr. Rajiv Saigal, moved to UCSF/ZSFG last year and is currently an active member and leader of the TRACK-SCI ZSFG team. Training of the CRC and enrollment has been very slow, and no participants have as yet been enrolled. The site is currently under review for reassessment of their membership in TRACK-SCI.

- Added University of Utah Medical Center as a site, including 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 is expected to begin this month.
- TRACK-SCI has continued to involve UCSF medical students, post-docs, residents, and fellows in data collection and analysis, including a PGY6 neurosurgery resident, Dr. Winward Choy, who worked for 6 months at BASIC on TRACK-SCI data curation and analysis.
- Progress towards ensuring continuing productivity of TRACK-SCI: Multiple grant applications have been submitted this past year that include some funds to support data collection and curation in TRACK-SCI. These include two funded DoD applications (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); a pending R61/33 biomarker discovery application to NINDS, also with Kyritsis as PI and Beattie and others as MPIs, and 3 DoD clinical trial applications being submitted this round by Dr. Rajiv Saigal and Co-Is on neuropathic pain treatment comparing transcutaneous and epidural spinal stimulation, and a second, multi-center grant on duraplasty as an acute treatment for SCI. These and other submissions are being coordinated to provide funding for TRACK-SCI CRCs and data specialists and some support for clinical and basic research personnel.

#### **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. This protocol is similar to that from the recent CAMPR study, which ZSFG/UCSF participated in, and the new CASPER study initiated by Dr. Brian Kwon. Drs. DiGiorgio and Saigal are the lead investigators for this study at ZSFG/UCSF, and patients enrolled in this new study will be co-enrolled in TRACK-SCI. The plans for evaluating duraplasty as an alternative and more aggressive method for controlling intra-spinal pressure form the basis of a DoD SCIRP LOI application that was accepted for submission. It is being submitted in the coming round with Dr. Rajiv Saigal as PI. 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- still on Zoom, but evolving slowly to include some on-site in-person meetings. Further impact is shown by our recent discussions with the Praxis SCI Institute, and with Dr. Kwon, concerning establishing 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**

As previously reported, UCSF Fresno has had severe issues related to COVID restrictions that were due in part to staffing issues and a general reduction in research activities including a change in the Neurosurgery staff within the department of Surgery. At this time, Dr. Yuh-Hung Kuo has left UCSF and there has been no suitable replacement. One CRC remains on the payroll and has been filling in missing data from the EMR system. Otherwise, activity at Fresno has ceased.

COVID-related restrictions on enrollment at ZSFG/UCSF were beginning to be lifted at the beginning of this year of funding, and we expected that return to full enrollment numbers would be attainable within a short time. This was, however, before the onset of the omicron variants surge, which began in December of 2021, with a first peak in January, 2022, subsequent decline, and then the .4 and .5 variants surge that is still ongoing, but declining in the SF Bay Area at this time. While there was a loosening of the restrictions on clinical enrollment at ZSFG during the last year compared to 2021, the continuing pandemic was associated with a dramatic reduction in SCIs and in consents to enroll, both at ZSFG/UCSF and at our site at Ohio State, and at the UCSF satellite at UCSF Fresno Medical Center, and Fresno endured staffing and other issues that impacted clinical research priorities, as reported above. We have had success in adding other centers to TRACK-SCI (not supported by this DoD award). These are reported in section 7 below.

## 6. PRODUCTS

Publications for this award since the last PR:

1. [Expert-augmented automated machine learning optimizes hemodynamic predictors of spinal cord injury outcome.](#)  
Chou A, Torres-Espin A, Kyritsis N, Huie JR, Khatry S, Funk J, Hay J, Lofgreen A, Shah R, McCann C, Pascual LU, Amorim E, Weinstein PR, Manley GT, Dhall SS, Pan JZ, Bresnahan JC, Beattie MS, Whetstone WD, Ferguson AR; TRACK-SCI Investigators.  
PLoS One. 2022 Apr 7;17(4):e0265254. doi: 10.1371/journal.pone.0265254. eCollection 2022.  
PMID: 35390006 **Free PMC article.**
2. [Decision tree-based machine learning analysis of intraoperative vasopressor use to optimize neurological improvement in acute spinal cord injury.](#)  
Agarwal N, Aabedi AA, Torres-Espin A, Chou A, Wozny TA, Mummaneni PV, Burke JF, Ferguson AR, Kyritsis N, Dhall SS, Weinstein PR, Duong-Fernandez X, Pan J, Singh V, Hemmerle DD, Talbott JF, Whetstone WD, Bresnahan JC, Manley GT, Beattie MS, DiGiorgio AM.  
Neurosurg Focus. 2022 Apr;52(4):E9. doi: 10.3171/2022.1.FOCUS21743.  
PMID: 35364586
3. [Appendicular Fracture and Polytrauma Correlate with Outcome of Spinal Cord Injury: A Transforming Research and Clinical Knowledge in Spinal Cord Injury Study.](#)  
Miclau 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
4. [Topological network analysis of patient similarity for precision management of acute blood pressure in spinal cord injury.](#)  
Torres-Espín A, Haefeli J, Ehsanian R, Torres D, Almeida CA, Huie JR, Chou A, Morozov D, Sanderson N, Dirlikov B, Suen CG, Nielson JL, Kyritsis N, Hemmerle DD, Talbott JF, Manley GT, Dhall SS, Whetstone WD, Bresnahan JC, Beattie MS, McKenna SL, Pan JZ, Ferguson AR; TRACK-SCI Investigators.  
Elife. 2021 Nov 16;10:e68015. doi: 10.7554/eLife.68015.  
PMID: 34783309 **Free PMC article.**

## 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. Total award +\$1,000,000.
- 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.
  - b. University of Utah School of Medicine, PI: Ramesh Grandhi.
- C. In addition, we are in 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.