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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 (UC Board of Regents)

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<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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### 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) 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

Accomplishments will be described in relation to overall goals and the final negotiated statement of work (SOW) as noted in “Tasks”.

Goals:

*Major Task 1, Yr1, Q1-3: Study initiation.*

*Establish Team meetings, onboarding of our consultants with lived SCI lived experience (SCI-LE).* At the official start date of August 01, 2020, TRACK-SCI had been operating since Aug 1, 2019 under a no-cost extension of the prior award, SC150198, which ended on July 31, 2020. Some TRACK-SCI personnel, and activities related to adding additional centers, were also being supported by year 4 of our “Center of SCI Research Excellence” award from the Craig H. Neilsen Foundation, which is described in section 7, “Participants and other collaborating organizations”.

IRB approvals for UCSF/ZSFG, UCSF Fresno, and OSUWMC sites. New guidelines for federal research mandate the use of a single IRB for multicenter studies. Although TRACK-SCI is exempt as it was initiated prior to this ruling, the UCSF IRB recommended following these guidelines when adding new centers. Therefore, in Sept 2020, the Smart-IRB account was set up and the UCSF site was designated the central IRB and the OSUMC application was prepared and submitted. On 9/28/2020, ZSFG protocol application was approved by the UCSF IRB, and in October OSUMC accepted reliance via the Smart-IRB. HRPO approvals were applied for UCSF/ZSFG and UCSF/Fresno, and in response to a request from HRPO, these documents were resubmitted. HRPO approval was obtained on Nov 6, 2020 and enrollment was open (COVID restrictions were however still in place- see below). In December, an IRB modification at UCSF was submitted for adding OSUMC as an external site. In January, the IRB approval was delayed by IRB staffing and technical issues.

Team meetings and the evolution of data sharing and project planning continued uninterrupted during the process of the IRB and HRPO approvals even though no new participants were recruited. All meetings were held using Zoom, and in fact the number of meetings was increased from bi-weekly to weekly, with alternate meetings designated as “Clinical research team” sessions (engaging the clinical care and research team as we had been doing in prior years) and “Data curation and analysis” sessions in which datasets and analytics specific to emerging projects are considered. The data meetings are open to all, but require the presence of the BASIC bioinformatics core team led by Dr. Ferguson. These meetings have evolved as critical drivers of progress in TRACK-SCI. As new projects emerge, these data meetings provide direction for curation and analysis planning. In addition, the planning of projects based on retrospective or limited prospective datasets that provide power calculations for planning, and data collection proceeds until the n is reached, then curation and analysis begin.

Note also the implementation of a new effort to keep TRACK-SCI datasets aligned with publications. Each publication is paired with a curated, de-identified dataset that is deposited in the SCI-CRUNCH repository under the Open Data Common for SCI (ODC-SCI) format. All TRACK-SCI datasets are carefully vetted to ensure the complete elimination of defined PHI. ODC-SCI is a web-based data repository supported by NIH and VA under separate funding with Adam Ferguson as PI. These meetings have driven a more consistent strategy for mining the accumulated data in TRACK-SCI.

Onboarding of TRACK-SCI consultants with SCI-lived experience: We have had the good fortune to recruit two consultants with SCI-lived experience, Dr. Paul Lu, Ph.D. (listed in the application as the designated consultant), is a neuroscience faculty member and spinal cord injury pre-clinical researcher at UCSD who Drs. Beattie and Bresnahan have collaborated with in the past. He has lived with paraplegia for many years and brings a unique perspective to our translational efforts to link the clinic and basic science research lab. Mr. Chris Barr was a participant in TRACK-SCI and was treated at ZSFG. He expressed interest in the project and has expertise in data analysis and programming. He is local, living in the Bay Area, and is a partial quad. Both have regularly attended the research and data meetings, contributing insights, and have developed as important members of the scientific team.

*Major Task 2: TRACK SCI Enrollment and Data Collection (Y1Q2- Y3)*

Enrollment and follow-up restrictions due to COVID-19: As of August 1, 2020, clinical research protocols at UCSF/ZSFG were operating under COVID-19 restrictions. TRACK-SCI is classified as 'category 3' clinical research at UCSF, which is defined as studies which do not directly benefit patient who are enrolled in the study. Category 1 is defined as COVID-19 specific studies, which remain unlimited; category 2 studies are those that are deemed to have some direct benefit (in at least one arm of the study). Category 3 clinical research activities at this time were limited to 12.5% of normal personnel density, and new enrollments were not allowed. In addition, restrictions on Emergency Department and ICU personnel densities precluded our clinical research coordinators (CRCs) from activity in those areas, and in-house patient follow-up visits (i.e. from participants enrolled during the prior year) were not allowed. However, follow-up surveys by phone were allowed and accomplished. UCSF guidelines changed on 09/17/2020 to allow up to 25% personnel density, but this did not allow for active enrollment, and indeed, the year-end COVID surge in San Francisco resulted in a return to 12.5% restrictions on 12/04/2020. Thus, from the initiation of the award until January, 2021, only a single participant had been enrolled. In the spring of 2021, COVID cases were diminishing in the SF Bay Area and California, and enrollment became possible. Yet the continuing pandemic was accompanied by an apparent reduction in trauma and SCI cases. Towards the end of the summer, the new delta variant had become the major driver of new cases, and additional restrictions were implemented. As a result, we have added 15 new participants (14 at UCSF, 0 at UCSF Fresno, and 1 at OSU) during the expansion phase (SC190233) of TRACK-SCI. However, we had plenty of data curation, analysis, and paper writing to keep the team occupied and consistent well attended Zoom meetings were maintained, resulting in considerable progress that included 5 new papers submitted or published.

*Major Task 3: Gene expression analysis and blood transcriptomics of enrolled TRACK SCI participants (Y1Q2- Y3)*

Add info from prior Q2 report. The procedures for preparing blood from patients at OSUWMC and for isolating RNA and shipping samples to UCSF were developed and communicated to the OSUWMC PIs and CRCs. We are ready to begin as enrollments commence.

*Major Task 4: Data analysis and dissemination*

Data curation and analysis of select outcome variables from the previous award are continuing as planned. Data from the RNA-sequencing for participants from the prior award is also continuing and the report on the initial cohort of 59 acute SCI cases plus trauma and healthy controls was completed, and the results were submitted for publication. These results have now been published as a BioRxiv preprint, and subsequently accepted and published in the March, 2021 edition of The Journal of Experimental Medicine. The lead author is Dr. Nikos Kyritsis

**(a) Human Use Regulatory Protocols**

**TOTAL PROTOCOLS:** 2 human subject research protocols are required to complete the Statement of Work.

**PROTOCOL(S):** (Activity for this year)

**Protocol ( 1 of 2 total):**

*Protocol [HRPO Assigned Number]:* E01545.1a

*Title:* Transforming Research and Clinical Knowledge in Spinal Cord Injury (ZSFG & OSU)

*Target required for clinical significance:* 250

*Target approved for clinical significance:* 250

**Submitted to and Approved by:**

- UCSF IRB approval for prospective observational study for this project was obtained.
- DOD HRPO approval obtained.
- Laguna Honda Hospital and Rehabilitation Center IRB approval obtained.
- OSU IRB reliance approval obtained.

**Status:**

*(i) Cumulative Progress:* This is an expansion of an existing project. The total study numbers for SCI patients at ZSFG are as follow: mean age = 56.2 (range 18-90); 2) spinal cord injuries at the cervical (107), thoracic (20), and lumbar (7) levels. 3) ASIA impairment scores at admission were A (n=18), B (n=9), C (n=12), D (n=35), unable to assess (e.g. comatose, drug impaired, etc) (n=60); 4) mechanism of injury was assault (n=14), fall (n=72), transport (n=37), and sports/leisure (n=4). Blunt injury (128); central cord cases (63); 5) concurrent traumatic brain injury (21); 6) median pre-hospital transport time was 16.0 min (range 2-49 min, n=80); 7) median total time in the ER was 252.5 min (range 37-1355 minutes, n=133); 8) median time to OR was 8.2 hours (range 0.7-267.7 hrs, n=94); 9) median hospital stay was 10.1 days (range 2.0-440.6 days, n=131). Subjects were discharged to acute rehab units (n=57), another hospital (n=47), home (n=19), deceased (n=8). Some three-month follow-up assessments have been completed (n=64), some six-month assessments (n=56), and some twelve-month assessments (n=58). So far we have recruited 15 healthy controls (4 female, 11 male), of mean age 54 (range 39-68); and 16 trauma controls (6 female, 10 male), of mean age 42.1 (range 22-94), with fractures, head lacerations, and blunt abdominal trauma. This prospective study is well underway and we expect to be able to continue to accrue patients for the rest of the grant period. The OSU site has recently obtained IRB approval and is now enrolling participants.

*(ii) Amendments submitted to the IRB and USAMRMC HRPO for review:* Submission 316360, OSU site PI change, University of Washington external site reliance, minor protocol changes (the UW site is not supported by SC190233, but this new site is included in the central IRB approval administered by UCSF).

*(iii) Adverse events or unanticipated problems involving risks to subjects or others and actions or plans for mitigation:* None.

**Protocol ( 2 of 2 total):**

*Protocol [HRPO Assigned Number]:* E01545.1b

*Title:* Transforming Research and Clinical Knowledge in Spinal Cord Injury (Fresno)

*Target required for clinical significance:* 120

*Target approved for clinical significance:* 120

**Submitted to and Approved by:**

- UCSF Prospective Study IRB Approval – UCSF IRB approval for prospective observational study for this project was obtained.
- DoD HPRO for UCSF has been obtained.
- Fresno IRB approval has been obtained.
- DoD HRPO approval for Fresno has been obtained.

**Status:**

*(i) Progress:* 58 subjects of the approved 120 (12 female, 46 male) with the following characteristics: 1) mean age = 45.6 (range 19-87); 2) spinal cord injuries at the cervical (n=36), thoracic (n=11) and lumbar (n=7) levels; 3) ASIA impairment scores at admission were A (n=13), C (n=8), D (n=17), E (n=1), and unable to assess (e.g. comatose, drug impaired, etc) (n=6); 4) mechanism of injury was assault (n=12), fall (n=21), transport (n=13),

sports/leisure (n=2), blunt injury (n=35), penetrating injury (n=13); 6) central cord cases (n=14); 7) concurrent traumatic brain injury (n=6); 8) mean pre-hospital transport time was 14.8 min (range 3-83 min, n=34); 9) mean time in the ER was 538.2 minutes (29-2186, n=50); 10) mean time to OR was 38.4 hours (range 0.3-231.3 hrs, n=37); 11) mean hospital stay was 14.4 days (range 2.9-63.6 days, n=50); 12) Subjects were discharged to acute rehab unit (n=27), another hospital (n=16), home (n=7), or deceased (n=2). Some three month follow-up assessments have been completed (n=19), some six-month assessments (n=21) and some twelve-month assessments (n=18). This prospective study is well underway and we expect to be able to continue to accrue patients for the rest of the grant period.

(ii) *Amendments submitted to the IRB and USAMRMC HRPO for review:* None.

(iii) *Adverse events or unanticipated problems involving risks to subjects or others and actions or plans for mitigation:* None.

#### **4. Impact.**

TRACK-SCI continues to publish high visibility papers derived from prior award data showing the usefulness of MRI evaluations, early surgery, and blood pressure management, and is influencing SCI clinical practices across multiple institutions. Presentations have been given at the American Spinal Injury Association meetings and the National and International Neurotrauma Societies annual meetings.

#### **5. Changes/Problems.**

No changes in protocols or goals, but due to COVID restrictions, we have been delayed in enrolling patients. We had changes in the site PI for Ohio State. Dr. Jan Schwab was replaced as PI by the head of neurosurgery, Dr. Frank Farhadi before enrollment began. Six months later, Dr. Farhadi was recruited to University of Kentucky, and was replaced as PI by Dr. ???.

#### **6. Products.**

Mummaneni N, Burke JF, DiGiorgio AM, Thomas LH, Duong-Fernandez X, Harris M, Pascual LU, Ferguson AR, Russell Huie J, Pan JZ, Hemmerle DD, Singh V, Torres-Espin A, Omondi C, Kyritsis N, Weinstein PR, Whetstone WD, Manley GT, Bresnahan JC, Beattie MS, Cohen-Adad J, Dhall SS, Talbott JF. Injury volume extracted from MRI predicts neurologic outcome in acute spinal cord injury: A prospective TRACK-SCI pilot study. J Clin Neurosci. 2020 Dec;82(Pt B):231-236. doi: 10.1016/j.jocn.2020.11.003. Epub 2020 Nov 25. PMID: 33248950

Kyritsis NK, Torres-Espin A, Schupp PG, Huie JR, Chou A, Duong-Fernandez X, Thomas L, Tsolinas RE, Hemmerle D, Pascual LU, Singh V, Pan JZ, Talbott JF, Whetstone WD, Burke JF, DiGiorgio AM, Weinstein PR, Manley GT, Dhall SJ, Ferguson AR, Oldham MC, Bresnahan JC, Beattie MS. (2021) Diagnostic Blood RNA profiles for human acute spinal cord injury. J. Exp. Med., 218 (3): DOI: <https://doi.org/10.1084/jem.20201795>.

Presentation at the National Neurotrauma society meeting, July 2021 (virtual): "Patient perspectives in SCI". Moderator, Dr. Adam Ferguson (UCSF). Person with life experience, Chris Barr (patient/consumer advocate, UCSF TRACK-SCI SC 190233); Neurosurgeon, Dr. Sanjay Dhall (head of spinal cord trauma, UCSF, Zuckerberg SF General Hospital and Trauma Center.

Presentation at the International Neurotrauma Society Symposium, Melbourne, Australia, Feb 8-11, 2021(virtual), Dr. Michael Beattie, "Acute care variables and blood transcriptomics to predict severity and outcomes in SCI: TRACK-SCI".

#### **7. Participants and other collaborating organizations.**

*A. Craig H. Neilsen Foundation support for TRACK-SCI:* onboarding OSUWMC (Francis Farhadi, MD and Jan Schwab, PhD site Co-PIs), University of Washington Neurosurgery (Rajiv Saigal, MD, PhD, PI). The Neilsen Foundations support for TRACK-SCI is from a special project award, "Center of Clinical Excellence for SCI", which is funded from 08/2016- 07/2022 (year 6 is an unfunded extension). This award provides some pilot funds for onboarding new sites, as well as salary support for 1 clinical research coordinator, 10% FTE for the PI, Dr. Beattie, and nominal (<10% FTE) for several clinical and research faculty associated with TRACK-SCI (Drs. Bresnahan-Neurosurgery, Ferguson-Neurosurgery, Dhall-Neurosurgery, Pan-Anesthesiology, Singh-Neurology/ICU, Talbott-Radiology, Whetstone-Emergency Medicine).