

# SCI 2020 Poster Session Abstracts

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**Poster #1: Improving upper extremity function of individuals with incomplete tetraplegia using transcranial direct current stimulation**

Tarun Arora<sup>1</sup>; Kelsey Potter-Baker<sup>2</sup>; Kyle O’Laughlin<sup>1</sup>; Xiaofeng Wang<sup>1</sup>; Manshi Li<sup>1</sup>; Frederick Frost<sup>1</sup>; Svetlana Pundik<sup>2</sup>; MaryAnn Richmond<sup>2</sup>; James Wilson<sup>2</sup>; Kevin Kilgore<sup>3</sup>; David A. Cunningham<sup>3</sup>; Anne Bryden<sup>3</sup>; Gail Forrest<sup>4</sup>; Steve Kirshblum<sup>4</sup>, Guang H. Yue,<sup>4</sup> Ela B. Plow<sup>1</sup>

*1. Cleveland Clinic Foundation, OH; 2. Louis Stokes VA Medical Center, Cleveland, OH; 3. Metro Health Rehabilitation Institute of Ohio, Cleveland, OH. 4. Kessler Foundation and Kessler Institute for Rehabilitation, West Orange, NJ*

Incomplete tetraplegia is the most common consequence after spinal cord injury (SCI) and currently over a 130,000 individuals are living with tetraplegia in the US. Regaining arm/hand function has been a top priority of individuals with tetraplegia. With the development of non-invasive methods of brain stimulation, the focus of rehabilitation is shifting towards utilization of these methods to restore function after SCI; however, there is a lack of strong evidence in their support. A previous pilot study in our lab found improvements in upper extremity muscle strength, dexterity grasp/grip function in 16 individuals with incomplete tetraplegia using a combination of transcranial direct current stimulation (tDCS; 2mA intensity) and upper extremity rehabilitation (tDCS+Rehab) for 20 hours (2 hours session x 5 sessions/week x 2 weeks). These improvements were greater than that seen with rehabilitation alone (sham + Rehab). Improvements were also seen in neurophysiologic measures as assessed using TMS.

We are now conducting a multi-site phase I/II randomized, sham-controlled, double-blinded clinical trial evaluating the safety, efficacy, and mechanisms of use of tDCS+Rehab in individuals with incomplete (AIS B/C/D) chronic tetraplegia (C2-C6 level). The clinical trial will be carried out at three sites nationwide: Cleveland Clinic, OH (lead site), VA Medical Centre, Cleveland, OH and Kessler Foundation and Kessler Institute of Rehabilitation, NJ and will involve a total of 44 patients.

We hypothesize that addition of tDCS to rehabilitation will be safe and feasible for stimulation of cortico-motor projections to the arm muscles in individuals with tetraplegia and will produce greater improvements in upper extremity function than rehabilitation given alone. We also expect that functional improvements will be associated with restoration of balance between corticomotor projections dedicated to the more affected muscle (Triceps) and the spared/less affected muscle (Biceps).

Enrolled participants will undergo baselines assessments at two different time points separated by a 3-week interval for study of any spontaneous shifts in metrics. After completion of baseline testing, participants will be randomly assigned to either receive tDCS+Rehab (experimental group; n=22) or Sham tDCS+ Rehab alone (control group; n=22) for 30 hours (2 hours session x 5 session/week x 3 weeks). Posttest assessments will be completed immediately after the end of treatment and a follow-up assessment will be completed after 3 months. Assessments will include measures of upper extremity impairment, activity and function. Neurophysiological measures will include TMS and Hoffman-reflex for study of neurophysiologic changes at supra-spinal and spinal levels, respectively. Twenty age and sex matched healthy control participants will also be enrolled to establish normal values of neurophysiological measures.

The study was approved for funding by the US Department of Defense (SCIRP) in fall 2017. Regulatory approvals have been sought from two of the three study sites. Study enrollment is expected to begin in February 2019.

## **Poster #2: Using the Computer Assisted Rehabilitation Environment to Simulate Real World Environments for Studying Manual Wheelchair Propulsion**

Sarah Bass BS<sup>1,2</sup>, Deepan Kamaraj MD, MS<sup>1,2</sup> and Alicia Koontz Ph.D., RET<sup>1,2</sup>

<sup>1</sup>*Human Engineering Research Laboratories, VA Pittsburgh Healthcare System, Pittsburgh, PA*

<sup>2</sup>*Department of Rehabilitation Science and Technology, University of Pittsburgh, Pittsburgh, PA*

Manual wheelchair propulsion has been studied for nearly four decades. Joint forces, motions and muscle activation have been extensively studied for level ground propulsion and propulsion on different types of surfaces such as carpet and tile. Ramped and cross sloped conditions have been studied to a much lesser extent and are two common terrains encountered by manual wheelchair users in the community. As a bigger push is made to take research out of the laboratory and into environments experienced daily by manual wheelchair users, there is still a lack suitable technology for studying wheelchair propulsion biomechanics on surfaces commonly encountered in the community. The challenge posed to researchers is how do we evaluate propulsion in more realistic environments while still maintaining the ability to accurately collect the necessary data?

As a step towards this goal, at the VA Pittsburgh Human Engineering Research Laboratories (HERL) we adapted the Computer Assisted Rehabilitation Environment (CAREN) (Motek Medical, Amsterdam, Netherlands) to study wheelchair propulsion. The CAREN is a novel system that combines a motion platform with split belt treadmill, virtual reality and synchronized biomechanics instrumentation including Smartwheels, force plates, 3D motion capture cameras, EMG, and physiological data collection. The CAREN system was originally designed for gait training and analysis. However, with a specialized set up and programming the CAREN has been adapted for studying wheelchair propulsion. Adaptations include wider treadmill belts, a customized tie down system to secure the wheelchair to the platform and a stair lift to gain access to the platform. Unlike other wheelchair treadmill set ups the CAREN has unique features that allow for better real-world simulations of community environments. The platform itself has six-degrees of freedom giving the ability to simulate a wide range of terrain encountered in the community such as hills/ramps and cross-slopes. Additionally, the treadmill belt allows the wheelchair user to select and modify their own pace while propelling. Compared to traditional wheelchair treadmills where the speed is pre-set and constant, the CAREN treadmill adjusts to accelerations, deceleration and changes in speed, thus allowing for more natural propulsion. The platform allows for study of reaction timing and responses to platform perturbations. Lastly, community environments can be simulated using the 180-degree virtual reality screen. In combination, these unique features make the CAREN an ideal tool for studying wheelchair propulsion biomechanics and simulating real world environments. Current research with CAREN is investigating the impact of varying wheelchair setups on ramp biomechanics. Future studies with the CAREN may include studying propulsion characteristics on cross slopes, looking at propulsion technique and adaptation when transitioning between different types of terrain, and investigating new training regimens or manual wheelchair designs in a safe environment before transitioning to real world.

### **Poster #3: Biomarkers of Spontaneous Recovery from Traumatic Spinal Cord Injury**

Ona Bloom, PhD, Paige Herman, MA Matthew Bank, MD Adam Stein, MD Peter Gregersen, MD Ashley Chory, MA

*The Feinstein Institute for Medical Research, Zucker School of Medicine at Hofstra/Northwell, Northwell Health*

Immediately after a SCI, a person confronts 3 major questions: (1) how much function have they lost, (2) what treatments promote recovery, (3) how much recovery of function can they expect over time? To answer the 1st question, a detailed medical exam tests movement and feeling throughout the body. The 2nd question is still largely unanswered: standard rehabilitation focuses on maximizing use of intact body parts and managing medical consequences of living with SCI. The 3rd question is also unanswered; there is no standard way to predict physical recovery, which occurs mostly within the 1st year after SCI. Surprisingly little is known about biological processes influencing recovery after SCI. This limits the development and advancement of medicines and other treatments for persons with SCI. One factor that may lead to less improvement in recovery of function is the inflammatory response to SCI.

From lab experiments, it is known that inflammation worsens the initial area of tissue damage and inhibits physical recovery after SCI. We and other researchers have also observed signs of inflammation in the blood of persons who are newly injured and persons living with SCI for years. Our long-term goal is to understand how inflammatory and other factors in the blood influence and/or predict recovery after SCI. Our hypothesis is that some inflammatory factors are higher in persons that have less physical recovery over time.

To test our hypothesis, we are conducting a study to measure if and how inflammatory and other genes in the blood change over time during the 1st year after SCI. Each participant has 4 study visits: within 0-3 days of their injury and then 3, 6 and 12 months later. At each visit, a small blood sample is collected and some health information, such as how the participant is able to perform activities of daily living, such as moving around or getting dressed.

While the study is ongoing, we performed a preliminary analysis of data from the first 2 participants who completed the study. Both participants had cervical level, neurologically incomplete injuries and were above age 65, typical of the growing older segment of the SCI population. We analyzed genes active in the blood and compared them to genes active in able-bodied persons and in persons living long-term with SCI. Interestingly, statistical methods that were blinded to who the samples came from were able to discriminate between the samples by injury status and by time since injury. We discovered at least one common inflammatory gene pathway that was significantly increased in all samples from persons with SCI. Additional samples from more participants are now being analyzed, so that we can investigate if inflammatory factors are higher in persons SCI and if the levels correlate with less physical recovery. While additional work will need to be performed to determine causality, it is hoped that the associative data from this study will help improve how to predict recovery after SCI and how to treat SCI in the future.

Support from: DOD SCIRP, NYSCIRB

#### **Poster #4: The Right to Science: Improving the Future of Spinal Cord Injury Research and Clinical Translation**

Anne M. Bryden MA, OTR/L<sup>1,2</sup>; Kimberly D. Anderson PhD<sup>1,3</sup>; Ali Arab PhD<sup>4</sup>; Mark Frezzo PhD<sup>5</sup>; Brian K. Gran PhD<sup>2</sup>; Theresa Harris JD<sup>6</sup>; M. Elise Johanson DPT<sup>7</sup>; William Lenart MS<sup>8</sup>

<sup>1</sup>*Institute for Functional Restoration, Case Western Reserve University, Cleveland, Ohio;* <sup>2</sup>*Department of Sociology, Case Western Reserve University, Cleveland, Ohio;* <sup>3</sup>*Department of Physical Medicine and Rehabilitation, MetroHealth Medical Center, Cleveland, Ohio;* <sup>4</sup>*Department of Mathematics and Statistics, Georgetown University, Washington, DC;* <sup>5</sup>*Department of Sociology, University of Mississippi, Oxford, Mississippi;* <sup>6</sup>*Scientific Responsibility, Human Rights and Law Program, American Association for the Advancement of Science, Washington, DC;* <sup>7</sup>*Palo Alto VA Medical Center, Palo Alto, California;* <sup>8</sup>*School of Engineering, Case Western Reserve University, Cleveland, Ohio.*

The human right to science may be a powerful resource to people with spinal cord injury (SCI). Despite exciting advances in research resulting in promising interventions, many technologies with proven benefits never become universally available due to commercial unsustainability in a market-based health care system. Article 15 of the United Nations (UN) International Covenant on Economic, Social, and Cultural Rights (ICESCR) articulates the right to enjoy the benefits of scientific progress and its applications. This project investigates the utility of the “Right to Science” as a framework for understanding the duties and obligations of consumers, scientists, health professionals and third-party payers in the provision of life enhancing interventions and technology for people with SCI. Can increasing human rights literacy among these stakeholders inspire creative and effective policies to improve research translation?

We have conducted preliminary work, supported by the Science and Human Rights Coalition (SHRC) of the American Association for the Advancement of Science (AAAS), investigating the attitudes of scientists and health professionals specializing in SCI concerning human rights. Primary findings from qualitative interviews indicated that most respondents were unaware of disability-relevant human rights doctrine. None were aware of the right to science as articulated in Article 15 of the ICESCR and all but one were not aware of the UN Convention on the Rights of Persons with Disability (CRPD). Only two respondents had previously considered injustices experienced by their clients with SCI as human rights violations, yet nearly all were intrigued by framing access difficulties within that paradigm. Overall, respondents reported they would find value in learning ways to implement human rights in their work. These findings are being used to develop an internet-based survey to query a broader segment of professionals specializing in SCI.

This cross-disciplinary work is relevant, complementing global efforts by AAAS to define the meaning of the Right to Science, as well as the UN’s current efforts at drafting a General Comment on the Right to Science. Relevant to SCI research and translation, Article 15 highlights the unacceptability of denying individuals access to products of science that are essential for lives of dignity. Additionally, it highlights the current paradoxical system in which discoveries based on public investment in research lead to economic benefits for private corporations. This is problematic for small populations such as SCI that do not generate large profits for private corporations. Increasing health professionals’ awareness of human rights doctrine and investigating its potential utility to promote access to needed technology is a precursor toward advocacy and policy change designed to improve the translational pathway.

Support: Science and Human Rights Coalition of the American Association for the Advancement of Science (AAAS)

## **Poster #5: Advanced MRI in Spinal Cord Injury: Preclinical and Human Studies**

Matthew Budde<sup>1</sup>, Shekar Kurpad<sup>1</sup>, Brian Schmit<sup>2</sup>, Kevin Koch<sup>1</sup>

<sup>1</sup>*Medical College of Wisconsin, Milwaukee, WI*; <sup>2</sup>*Marquette University, Milwaukee, WI*

The main projects currently underway are:

- 1) Acute patient SCI: Specialized diffusion weighted MRI of the acutely injured spinal cord to improve detection of injury severity and prediction of neurological outcomes.
- 2) Acute rodent SCI: Development of noninvasive perfusion MRI methods to monitor blood flow in the acutely injured rodent spinal cord as a complement to diffusion MRI to detect the penumbra vulnerable to secondary injury.
- 3) Chronic patient SCI: Metal artifact-reducing MRI to monitor the long-term effects of spinal cord injury and follow-up after surgical stabilization hardware.

The overall goal of these projects is to enable better detection of spinal cord injury with an emphasis on the acute care setting. Advanced MRI has dramatically improved clinical management in other acute disorders such as cerebral ischemia and traumatic brain injury, yet similar technologies are not as common in the injured spinal cord due to the difficulties and complications of imaging the cord. These projects are primarily focused on new methods of acquiring MR images of the spinal cord with an emphasis on novel diffusion and perfusion contrasts with translational potential. Our previous and ongoing projects involving animal MRI are open to collaboration and sharing of resources in the form of MRI software 'pulse sequences' and accompanying analysis software freely available to outside investigators. The human studies are open to collaborative efforts or multi-center studies. Collaborations with other teams involved in diagnostics including imaging (MRI, CT, ultrasound), biomarkers (blood/CSF), or pressure and blood flow monitoring (catheters) would be particularly welcome. The long-term goal is to provide the research community and medical care teams with better tools to detect and visualize spinal cord injury in order to promote the development of therapies and improve patient outcomes after SCI.



**Poster #6: Using Knowledge Translation to Develop Free Research-Based Resources to Support People Living with Spinal Cord Injury and Their Families**

Xinsheng "Cindy" Cai, PhD, Steven Garfinkel, PhD, Delphinia Brown, PMP, Amber Hammond, MS, Jeremy Rasmussen, MA, Merykokeb Belay, BS, Debbie Davidson-Gibbs, MS, and Aynura Berdyeva, BS

*Model Systems Knowledge Translation Center (MSKTC)*

The goals of the Model Systems Knowledge Translation Center (MSKTC) are to (1) enhance understanding of spinal cord injury (SCI), traumatic brain injury (TBI), and burn injury (Burn) rehabilitation research; (2) increase awareness and use of SCI, TBI, and Burn Model Systems research findings by appropriate stakeholders; and (3) centralize SCI, TBI, and Burn Model Systems resources for effective and uniform provision of training, technical assistance, and dissemination; and increase capacity of Model System grantees to engage in knowledge translation (KT) activities.

Although the Model Systems Knowledge Translation Center (MSKTC) engages stakeholders to make SCI, TBI, and Burn research useful and easy-to-understand by people with disabilities, their caregivers, and other stakeholders, the poster will focus on how the MSKTC has engaged SCI stakeholders in translating SCI research for consumers. The poster will highlight user needs studies, cognitive testing, product development, dissemination, and other knowledge translation strategies. It will also feature SCI resources such as factsheets, videos, and other products that support community living and participation, health and function, and employment for individuals with SCI. In addition, the poster will describe the key components of the SCI Model System Program funded by National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR), Administration for Community Living, US Department of Health and Human Services.

The MSKTC has established a website at <https://msktc.org/> that draws around one million visitors a year with its large collection of free research-based and consumer-friendly resources on SCI, TBI, and Burn. The SCI resources at <https://msktc.org/sci> cover a wide range of topics such as skin care and pressure sores, spasticity, pain management, bowel function, bladder management, urinary tract infection, respiratory health, sexuality, safe transfer technique, sports and recreation, adjusting to life, dysreflexia, depression, driving, employment, exercise, gait training, pregnancy, surgical alternatives for bladder management, and a wheelchair series. To meet the diverse learning needs of stakeholders, these resources are in print, audio, and visual formats. The MSKTC website also includes resources on Model System centers and the Model System longitudinal database. The MSKTC will continue to work with Model System researchers, consumers, and other stakeholders to develop resources supporting people living with SCI, TBI, and Burn.

## **Poster #7: Progression and Recovery of Traumatic Spinal Cord Injury Assessed by Multiparametric MRI in Non-human Primates**

Li Min Chen, Feng Wang, Pai-Feng Yang, Tung-Lin Wu, Arabinda Mishra, Qing Liu, Nellie Byun, John C Gore.

*Vanderbilt University Institute of Imaging Science, Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center*

The spinal cord (SC) undergoes dynamic changes in function, structure, and tissue composition after injury, and over time, during recovery. Some of these changes are believed to mediate recovery through unknown mechanisms, so they are potential targets for therapeutic interventions that enhance recovery. These dynamic changes have not until recently been detectable non-invasively. Despite the technical challenges of imaging the spinal cord in vivo we have successfully developed multiparametric MRI methods that permit longitudinal monitoring of changes in the functional integrity of intraspinal circuits (via functional MRI), demyelination and remyelination of individual white matter tracts (via Diffusion Tensor Imaging, DTI and Quantitative Magnetization Transfer, qMT), and concentrations of metabolic and neurotransmitters (such as glucose and glutamate) in spinal tissue (via Chemical Exchange Saturation Transfer, CEST). These MRI metrics permit a fine-scale and comprehensive analysis of spinal pathology at the injury site and along the cord within a single examination, which no previous method afforded. This capability provides unprecedented opportunities for pre-clinical as well as clinical research.

Our studies, supported by NINDS, represent the first attempts to detect and interpret resting state fMRI signals in the spinal cords of monkeys. The monkey SC is an excellent model of the human SC and allows for the study of intrinsic neural circuits that are currently poorly understood yet represent an essential feature of normal function which are affected by spinal cord injuries. The monkey work is particularly significant given our recent findings that such functional connectivity can be detected in human SCs; however, the necessary fundamental studies are precluded in humans by safety and ethical constraints. The studies are also significant in the context of recent developments in methods for promoting SC recovery and the acknowledged need to develop safe and effective means for monitoring interventions to improve spinal cord repair. We have shown that measurements of fMRI connectivity of intraspinal circuits are sensitive indices of the integrity of spinal cord function. The recovery of functional connectivity (FC) between spinal grey matter horns correlated strongly with improvements in sensorimotor behavior, indicating its potential as a useful biomarker of SC function.

A separate project supported by the DoD explores the potential of multiparametric MRI as imaging biomarkers of spinal cord injury and recovery. In addition to function, we have used MRI to detect demyelination and remyelination processes in injured and recovering white matter tracts and traced the dynamic changes associated with behavioral recovery in monkeys with cervical SC injury. Our ultimate goals are to determine the sensitivity and specificity of each MRI metric in probing the underlying pathology, as well as the functional, structural and chemical markers essential for recovery, and to establish their roles as biomarkers for assessing outcomes of therapeutic interventions.

In summary, our group has developed high-resolution quantitative MRI metrics that are sensitive for detecting and monitoring functional and structural changes in the spinal cord after injury and, over time during recovery in non-human primates (NHP). Our long-term goals are to translate imaging biomarkers of functional recovery identified in SCI models in NHPs to applications in SCI patients, and to use these biomarkers as objective assessments for evaluating outcomes of therapeutic interventions. We are seeking collaborators who are interested in applying these non-invasive MRI biomarkers in their preclinical and clinical studies involving spinal cord injury. patients, and to use these biomarkers as objective assessments for evaluating outcomes of therapeutic interventions. We are seeking collaborators who are interested in applying these non-invasive MRI biomarkers in their preclinical and clinical studies involving spinal cord injury.

**Poster #8: National Spinal Cord Injury Statistical Center: [www.uab.edu/nscisc](http://www.uab.edu/nscisc)**

Yuying Chen, MD, PhD; Michael DeVivo, DrPH; Victoria Allen, MPH; Galina Waites, MS; Troy Bland, BS; and Phillip Klebine, MA

*Department of Physical Medicine and Rehabilitation, University of Alabama at Birmingham, Birmingham, Alabama, USA*

*What is the National SCIMS Database?*

The database has been in existence since 1973 and currently captures data from an estimated 6% of new spinal cord injury (SCI) cases every year in the US. Since its inception, 29 federally funded SCIMS centers have contributed data to the database. As of September 2018, the database contained information on 33,406 persons with SCI. This makes it the world's largest and longest active SCI research database and the world's most extensive source of available information about the characteristics and life course of individuals with SCI. There are individuals enrolled into the database who have now been followed for 45 years after injury.

*What are the objectives of the National SCIMS Database?*

Data from the database is intended to: 1) identify demographics and the use of services by individuals with SCI; 2) examine specific rehabilitation, health and life course outcomes of SCI; 3) establish expected rehabilitation treatment outcomes for SCI; 4) identify and evaluate trends over time associated with SCI; and 5) serve as a resource for conducting historical, prospective, and longitudinal SCI-related research.

*How to access data from the National SCIMS Database?*

The NSCISC welcomes the use of data for the purposes of improving the lives of persons with SCI. De-Identified data collected before October 1, 2016 are freely available for download from the NSCISC web site ([www.uab.edu/nscisc](http://www.uab.edu/nscisc) under the "Database and Public Access" tab). De-Identified Data are stripped of all identifiers defined by the Health Insurance Portability and Accountability Act (HIPAA). A limited data set collected before and after October 1, 2016 is also available to independent researchers and those seeking SCIMS comments or collaboration. A limited data set is stripped of all HIPAA-defined identifiers except age, dates, city, state or zip. Obtaining a limited data set requires data request proposal, SCIMS review and approval, IRB approval, and data use agreement.

*What are other resources at NSCISC?*

The NSCISC provides consultation and technical assistance to investigators who are interested in analyzing data from the National SCIMS Database for research. Based on new data from the database, on an annual basis, the NSCISC website publishes "Facts and Figures at a Glance" and an extensive statistical report. Currently, there are 2 interactive search tools available on the NSCISC website under "Quick Tools" tab for the public to query statistics of the leading causes of SCI and life expectancy after SCI. To assure comparability and reliability of data obtained across SCIMS centers, the NSCISC has established rigorous criteria and quality control procedures for information collected for and entered into the database. These standardized operating procedures, policies, and guidelines can be easily adopted by other data registries and databases.

*Funded by the National Institute on Disability, Independent Living, and Rehabilitation Research and operated from the University of Alabama at Birmingham, the National Spinal Cord Injury Statistical Center (NSCISC) supports and directs data collection, management, analysis, and public accessibility of the National Spinal Cord Injury Model Systems (SCIMS) Database.*

## **Poster #9: Regulation of Spinal Cord Regeneration in Zebrafish**

V Cigliola, N Lee, KD Poss

*Department of Cell Biology, Regeneration Next, Duke University Medical Center, Durham, NC 27710, USA*

Spinal cord injury is a devastating condition in which massive cell death and disruption of neural circuitry lead to long-term chronic functional impairment and paralysis. Developing strategies to treat and reverse spinal cord injury is one of the main goals in regenerative medicine. The mammalian spinal cord shows a poor spontaneous regenerative response after damage. In stark contrast, after spinal cord transection in adult zebrafish, a striking glial cell response occurs, leading to the formation of a tissue bridge between the two spinal cord ends and facilitating functional recovery. While some spinal cord regeneration genes have been identified, the regulatory sequences that turn on and off these genes during regeneration are still unknown. Here, employing techniques allowing identifying changes in chromatin accessibility upon spinal cord injury, we define atlases of sequences becoming more accessible to transcription factors, thereby controlling gene expression, during regeneration. We developed a system to screen hundreds of accessible regions in vivo in zebrafish and identify some able to switch on gene expression in and around the injury area. These findings will advance our understanding of how zebrafish spinal cord regeneration occurs and are relevant to approaches for understanding and manipulating mammalian spinal cord regeneration.

## Poster #10: Abilities Research Center

*Mar Cortes, MD, co-Director Abilities Research Center, Department of Rehabilitation & Human Performance (Mount Sinai, NY); David Putrino PhD, Director of Innovation, co-Directors Abilities Research Center, Department of Rehabilitation & Human Performance (Mount Sinai, NY); Adam Fry postdoc, Abilities Research Center, Department of Rehabilitation & Human Performance (Mount Sinai, NY)*

*Icahn Medical School at Mount Sinai*

The Abilities Research Center (ARC) is a place that brings together scientists, clinicians, engineers, artists and story-tellers with one collective goal: using technology to help individuals perform better. Despite the best know rehabilitation methods the incomplete recovery of function after spinal cord injury remains a major problem. The development of novel therapeutic strategies and the use of combined therapies will be the present and future of SCI rehabilitation. Our center has the capability to address some of these important questions. Promoting innovation in neurorehabilitation:

- Dr Putrino develops innovative technology-based solutions for individuals in need of more accessible and higher quality healthcare. He conducts clinical trials of novel technologies to investigate their effectiveness at reducing and tracking symptoms in various patient populations.
- Dr Cortes research focuses on how to activate, modulate and reorganize brain and spinal networks in order to restore motor function in people affected by neurological disorders. In her studies, she couples state-of-the-art robotic technology and non-invasive brain and spinal stimulation techniques to understand the mechanisms of motor dysfunction and improve motor recovery.

**Big picture:** The aims of the ARC are to use state-of-the-art technologies to:

- understand human voluntary movement in health and after neurological damage,
- develop innovative and disruptive strategies for addressing the sensory, motor and psychosocial consequences of neurological injury and disease
- rapidly accelerate the path of these technologies from scientific concept to mainstream clinical adoption as quickly as is feasible.

**Research methods/tools:** The ARC has two major focus: developing innovative technology-based solutions for individuals in need of more accessible and higher quality healthcare; and understanding the underlying mechanisms of motor dysfunction and enhance motor recovery after spinal cord injury in humans by using the following approaches:

- a. The use of neurophysiology (transcranial magnetic stimulation, TMS), to investigate a) the functional integrity of the corticospinal system, as well as b) the specific pattern of reorganization in the primary motor cortex (TMS mapping) at chronic stages or during the rehabilitation process, and c) the spinal circuitry, by studying the H-reflex and its implication in motor recovery.
- b. The use of neuromodulatory interventions with the aim of strengthening the preserved corticospinal connections below the level of the injury by targeting either the brain (using transcranial direct current stimulation, tDCS) or the spinal cord (using repetitive TMS combined with electrical stimulation).
- c. The use of repetitive behavioral interventions such as the use of robotic devices or exoskeletons able to deliver precisely controlled high-dose therapy, as well as to objectively and reliably quantify motor dysfunction.

### **Current project status/next steps:**

The Abilities Research Center (ARC) recognizes that innovation is required to improve access to high quality healthcare, globally. We partner with leaders in industry, engineering, science, clinical practice and (most importantly) patients with the passion and capabilities to dramatically improve the standards of care for people everywhere.

Some example of our research studies are:

- Virtual reality to improve chronic neuropathic pain in people with spinal cord injury
- Safety and Efficacy of Autologous Cell Therapy combined with intensive rehabilitation and non-invasive electrostimulation as a treatment to repair traumatic spinal cord injury
- Walking Improvement for SCI with Exoskeletons

- Non-invasive stimulation for improving motor function in spinal cord injury: The combination of central magnetic stimulation (corticospinal tract) and peripheral electrical stimulation (Ia afferent) targeting the spinal cord can modify the spinal circuitry (H-reflex) and motor performance when applied in a synchronous manner.
- Combined transcranial direct current stimulation and hand robotic training in chronic SCI

## Poster #11: Developing a Spinal Reflex Conditioning System for Clinical and Research Use

Amir Eftekhar<sup>1</sup>; Aiko Thompson<sup>2</sup>; Richard Segal<sup>2</sup>; Christina Gill<sup>2</sup>; James J.S. Norton<sup>1</sup>; Susan M. Heckman<sup>1</sup>; Theresa M. Vaughan<sup>1</sup>; Timothy Fake<sup>1</sup>; Isaac Clements<sup>3</sup>; Anna Harrison<sup>3</sup>; and Jonathan R. Wolpaw<sup>1,4</sup>

<sup>1</sup>National Center for Adaptive Neurotechnologies, Wadsworth Center, NY State Department of Health, Albany NY;

<sup>2</sup>National Center of Neuromodulation for Rehabilitation, Medical University of South Carolina; <sup>3</sup>Axion Biosystems, Atlanta GA; <sup>4</sup>Department of Neurology, Stratton VA Medical Center, Albany, NY.

Over the past several decades, animal and human research led by our laboratories has developed and validated a powerful new noninvasive therapy that can target beneficial change to specific spinal reflex pathways (e.g., Eftekhar et al. 2018). Through an operant conditioning protocol, the patient learns to modify the brain's descending control over a selected reflex pathway. Over a series of one-hour sessions, this modified descending control gradually changes the spinal reflex pathway itself. Thus, it can restore a more normal reflex. Furthermore - and most important - this focused change triggers beneficial plasticity in other pathways as well. It can thereby improve key functions such as locomotion. In animals and people with chronic incomplete SCI, spinal reflex conditioning can increase walking speed and reduce limping. These improvements are apparent to people in their daily lives, and they persist after treatment ends. The wider exploration of spinal reflex conditioning's clinical value requires a concerted effort across multiple research labs and clinics. This endeavor is now impeded by a complex laboratory system that limits spinal reflex conditioning to use by highly trained experts. We need a robust clinically practical spinal reflex conditioning system that is user friendly and can be widely disseminated. This system should be able to support conditioning protocols that target other reflex pathways (e.g., upper limbs), and protocol modifications that increase the rate of reflex change (e.g., by combining conditioning with other therapies).

The National Center for Adaptive Neurotechnologies and the National Center of Neuromodulation for Rehabilitation are working together with industry and clinical translation partners to develop and test such a system. This system incorporates new software to: automate the selection of stimulation and recording sites; derive M-wave/H-reflex recruitment curves; select and adjust stimulus and conditioning parameters; and collect, analyze, and present data to the therapist. In addition, the new system includes software for system error checking and usage reporting to facilitate therapist training and clinical quality control. We are working with industry partners Axion Biosystems to incorporate Axion's propriety recording, stimulation, and electrode array technology into this new system. This interface technology, combined with new software, can automate the process of identifying recording and stimulation sites, and thus further simplify spinal reflex conditioning.

Finally, we are working with the NIH-supported Center for Translation of Rehabilitation Engineering Advances and Technology to define our clinical translation pathway. In accord with this pathway, we have established formal collaborations with major clinical centers (MUSC, MedStar NRH, Helen-Hayes Hospital) to define the potential clinical range and enhance the clinical efficacy and practicality of our conditioning protocols. In sum, we anticipate that this work will have major impact. The new system will enable clinicians and researchers elsewhere to participate in the further development, comprehensive evaluation, and dissemination of operant conditioning protocols that produce targeted plasticity and can thereby complement traditional therapies and enhance recovery of function for people with SCI.

## **Poster #12: Exploring neuromodulatory approaches in acute and chronic SCI**

Stephen Estes<sup>1</sup>, Anastasia Zarkou<sup>1</sup>, Jennifer Iddings<sup>1</sup>, Jasmine Hope<sup>2</sup>, and Edelle Field-Fote<sup>1,2,3</sup>

*1. Spinal Cord Injury Research Lab, Crawford Research Institute, Shepherd Center; 2. Emory University; 3. Georgia Institute of Technology, Atlanta, GA*

Following a spinal cord injury (SCI), the direct line of communication between the brain and body is disrupted. The loss of signals traveling from the brain to the body as well as the loss of sensory signals traveling from the body to the brain, which are important for informing the brain on what the body is experiencing, impairs motor control. This impairment limits independence in the performance of daily activities, decreasing the quality of life in persons with SCI.

While conventional electrical current in the form of functional electrical stimulation (FES) has long been used as part of rehabilitation protocols, newer approaches use stimulation to strengthen the remaining connections between the brain and the spinal cord for improved function. In particular, these approaches can target sensory inputs (i.e. whole-body vibration - WBV, stochastic resonance - SR, and transcutaneous spinal cord stimulation - tcSCS) or they can act directly on the brain (i.e. non-invasive brain stimulation approaches like transcranial direct current stimulation - tDCS, and transcranial random noise stimulation- tRNS) to promote functional performance. Further, these non-invasive stimulation approaches are low-cost, simple to administer, and can be utilized by clinicians to improve the outcomes of traditional training strategies. In the SCI Research Laboratory at Shepherd Center, we are currently exploring the effects of these novel stimulation approaches, when combined with practice and training, to improve hand function and walking ability as well as reduce spasticity in individuals with SCI.



**Poster #13: OPEN DATA COMMONS FOR SPINAL CORD INJURY (ODC-SCI.org): COMMUNITY-DRIVEN DATASHARING INFRASTRUCTURE FOR RESEARCH**

Ferguson AR<sup>1,10\*</sup>, Almeida C<sup>1</sup>, Beattie MS<sup>1</sup>, Bixby JL<sup>2</sup>, Bresnahan JC<sup>1</sup>, Callahan A<sup>3</sup>, Grethe JS<sup>4</sup>, Haefeli J<sup>1</sup>, Huie JR<sup>1</sup>, Lemmon VP<sup>2</sup>, Martone ME<sup>4</sup>, Magnuson DSK<sup>5</sup>, McTigue D.M.<sup>6</sup>, Nielson JL<sup>7</sup>, Popovich PG<sup>6</sup>, Schwab JM<sup>6</sup>, Tetzlaff W<sup>8</sup>, Torres-Espin A<sup>9</sup>, Fouad K<sup>9\*</sup>

\*Co-presenters

*1) Brain and Spinal Injury Center (BASIC), University of California San Francisco; 2) University of Miami Miller School of Medicine; 3) Stanford University; 4) Neuroscience Information Framework (NIF), University of California San Diego; 5) University of Louisville; 6) Ohio State University; 7) University of Minnesota; 8) University of British Columbia; 9) University of Alberta; 10) San Francisco VA Medical Center*

Spinal cord injury (SCI) involves changes to the cellular, molecular, and tissue integrity of the spinal cord. SCI results in loss of motor control and mobility, sensory and autonomic dysfunction. The complexity of SCI and collinearity of symptoms limit reproducibility of findings across laboratories and translation of new treatments from the bench to the bedside. The SCI research field has a 'big-data' problem; there are too many variables, metrics, and symptoms associated with SCI to identify a single mechanistic target that generalizes across the full heterogeneity of the SCI syndrome. Modern analytics, machine learning, and contemporary data science tools have the potential to enable researchers to query and extract patterns from complex data to form hypothesis and make new discoveries. To use these tools large volumes of data are needed, requiring sample sizes exceeding those typically collected within a single laboratory. Thus, a major barrier to realizing the potential of data science has been a cultural skepticism to data sharing. In the past 8 years the SCI research community has demonstrated a strong willingness to share data and work collaboratively, pooling data across 13 laboratories to form the VISION-SCI repository, now housing subject-level data from over 3000 rodents with SCI. A collective of SCI researchers is now focused on building a scalable, structured data sharing platform that enables users to upload, query, and download data: the Open Data Commons for Spinal Cord Injury (<http://ODC-SCI.org>), a partnership with the Neuroscience Information Framework (part of the NIH Neuroscience Blueprint Initiative). The ODC-SCI accommodates raw data underlying published figures as well as data and metadata that are unpublished. The portal helps harmonize and democratizes data, and grants users access to large volumes of data that are otherwise inaccessible helping achieving the data stewardship of making SCI data Findable, Accessible, Interoperable, and Resusable (FAIR). At the time of writing the ODC has 127 users, 39 registered laboratories and 107 datasets. With continued growth the ODC has potential to improve reproducibility across laboratories, and hasten new discoveries within SCI research with a data-driven approach.

Supporters: Craig H. Neilsen Foundation, Wings for Life Foundation, International Spinal Research Trust, Rick Hansen Institute, International Neuroinformatics Coordinating Center (INCF), UCSF-BASIC, University of Alberta, NIH/NINDS, VA

## **Poster #14: DIAPHRAGM PACING TO INCREASE RESPIRATORY FUNCTION AND RECOVERY AFTER CERVICAL SPINAL CORD INJURY**

Emily J. Fox<sup>1,3</sup>, Kathryn Cavka<sup>3</sup>, Paul Freeborn<sup>3</sup>, Geneva Tonuzi<sup>3</sup>, Andrew Kerwin<sup>2</sup>, Chasen Croft<sup>2</sup>, Anatole D. Martin<sup>1</sup>, David Fuller<sup>1</sup>

<sup>1</sup>University of Florida, Department of Physical Therapy, Gainesville, FL; <sup>2</sup>UF Health, Gainesville and Jacksonville, FL; <sup>3</sup>Brooks Rehabilitation, Jacksonville, FL

**Project background and goals:** Cervical spinal cord injury (CSCI) causes severe respiratory impairment and the resulting complications are a leading cause of illness and death. Although mechanical ventilation (MV) is lifesaving, MV use is associated with diaphragm atrophy and high respiratory infection rates. Intramuscular diaphragm stimulation, or diaphragm pacing (DP), is now used acutely to promote weaning from MV. Preliminary reports suggest that DP may have a rehabilitative effect, improving diaphragm activation, respiratory function, and promoting recovery of independent respiration. The effects of DP, however, have not been systematically evaluated. Therefore, the goal of this research project was to test the hypothesis that DP increases diaphragm activation and improves respiratory function.

**Research methods and results:** Ten adults with acute, traumatic CSCIs (5 males, mean age 42.9±12 years; mean time post injury 16.7±10.2 days) who recently underwent implantation of DP wires due to failure to wean from MV provided informed consent to participate. Injuries were classified as C1 to C4, American Spinal Injury Association Impairment Scale A or B (motor complete, n=9) and C (motor incomplete, n=1). Respiratory function and voluntary diaphragm activation were assessed within 3 days post implantation of the DP wires and assessments were repeated at regular intervals up to four months post DP implantation. Respiratory function was assessed using standard measures of tidal volume (Vt), forced vital capacity (FVC), and maximal inspiratory and expiratory pressures (MIP, MEP). Diaphragm activation was assessed by recording electromyograms (EMGs) from the intramuscular DP wires during maximal inspiratory maneuvers. All tests were conducted without assistance from DP and with the lowest ventilator setting tolerated. Following onset of DP, 8 of 10 individuals weaned from MV (mean time 35±24 days) and 6 individuals resumed independent respiration without use of DP. All measures of respiratory function increased over time (p<0.05). Average gains in respiratory function were: Vt, +23±22% (range -21 to 61%); FVC, +42±16% (range 17 to 64%); MIP, +43±56% (range -46 to 124%); MEP +67±64% (range -31 to 176%). Mean peak EMG burst amplitude during maximal inspiratory maneuvers increased 20% (range 0 to 92%).

**Project status:** Study outcomes indicate that following initiation of DP, adults with severe CSCIs demonstrated gains in respiratory function and diaphragm activation. Nearly all individuals weaned from MV and over half progressed to independent respiration. Outcomes suggest that DP may be useful for promotion of respiratory function and recovery after CSCI. Stimulation of the diaphragm is likely to promote muscle health and also may induce neuroplastic changes in the respiratory neural control system. Improving respiratory function after CSCI is critical for reducing dependence on MV and improving health and functional outcomes after SCI. The short-term next step for this project is to examine the effects of DP on diaphragm activation during tidal breathing to further understand the impact of DP on diaphragm activation. Next steps also include examination of DP-induced changes in the respiratory neural control system following CSCI.

**Funding:** Craig H. Neilsen Foundation; NIH/NICHHD K12 HD055929

## **Poster #15: Harnessing online connectivity for good: Using a virtual platform to promote exercise adoption among those with SCI**

Katherine Froehlich-Grobe, PhD; Amber Lopez, MPH-PAPH; Christa Ochoa, MPH; Rita Hamilton, DO; Simon Driver, PhD

*Baylor Scott & White Institute for Rehabilitation, Dallas, TX*

**Background:** While many people struggle to maintain an active lifestyle, individuals with spinal cord injury (SCI) face unique barriers to starting and maintaining an exercise routine. Available interventions to promote increased activity in

this population are limited, but important to help increase independence and quality of life. To address this gap, we developed an intervention program to guide people with SCI to adopt and sustain regular exercise by increasing the accessibility of knowledge and support to those living with SCI. This study is designed to address whether evidence-based approaches that have been adapted to address the unique issues facing those with SCI and informed by theory to teach behavioral skills can be successfully delivered over the internet.

**Methods:** Our intervention includes a website with 16 learning modules, corresponding to each week of the intervention. Participants meet weekly as a group via teleconference with study staff members to discuss the material covered and to complete a skill-building activity together. Topics and activities are focused on behavioral change and gradual progression towards a goal of at least 150 minutes of moderate physical activity per week. Participants receive a starter package of basic exercise equipment to begin their exercise program (aerobic activity and strength training), plus a Polar activity tracker and heart rate monitor to track each exercise bout. Self-monitoring skills are encouraged and reinforced through the Polar device which can provide real-time feedback on number of minutes spent on physical activity. Primary outcomes are intervention engagement and time spent in exercise each week over 16 weeks. Participants located within the Dallas-Fort Worth area are also asked to complete pre- and post-intervention fitness testing.

**Results:** Interim results after randomizing 49 people, 20 of whom completed the online program show that 80% set formal exercise goals and 65% later updated their goals. Initial goals targeted performing aerobic activity an average of 4.5 days per week for an average of 144.7 minutes. Week 11 updated goals reveal an average increase of 26.8 minutes in aerobic time. These goals show that most people planned to do home workouts (68.8%), but half (50%) also planned gym workouts. Three-quarters

(75%) completed the online activity to anticipate potential barriers and develop plans to get back on track. Commonly identified barriers included work, health events, lack of sleep and energy. Most participants (65%) synced their Polar data, which indicated participants engaged in an average of 42 minutes per week at an average heart rate of 125 beats per minute. Retention over the 16-week program is 79% to date.

**Current Project Status and Next Steps:** The project is currently delivering the intervention to the last 2 randomized cohorts and is expected to conclude data collection later this year. While the interim data have shown promising results regarding participant engagement and retention, effectiveness will be examined through analysis of pre- and post-intervention activity level, both self-reported (through survey data) and objective (through Polar exercise data) as well as fitness levels at baseline and post-intervention.

## **Poster #16: Reanimating Sensory and Motor Hand Function Using a Neural Bypass Brain-Computer Interface**

Patrick Ganzer, Sam C. Colachis, Mike A. Schwemmer, Dave A. Friedenberg, Carly E. Swiftney, Adam F. Jacobowitz, Doug J. Weber, Marcia A. Bockbrader, Gaurav Sharma

*Battelle Memorial Institute, The Ohio State University (Center for Neuromodulation & Department of Physical Medicine and Rehabilitation), University of Pittsburgh (Department of Bioengineering)*

The project goal of this research is to reanimate sensory signals from the hand that become subperceptual following a spinal cord injury (SCI) while simultaneously reanimating motor function using a brain-computer interface (BCI) to augment overall sensorimotor function. The sense of touch is a key component of motor control. Unfortunately, the vast majority of BCI systems do not yet incorporate sensory feedback. Recent observations by our group indicate that residual hand sensory information is transmitted to the brain, can be decoded from motor cortex during movement, and boosted into conscious perception to enhance the sense of touch using a BCI.

The research experiments conducted for this study were performed with a participant who has a cervical SCI, operating at a C5/C6 level of sensory perception. The participant has an intracortical recording array implanted in left primary motor cortex (M1) and has extensive experience using a BCI for motor reanimation of the hand. The BCI reanimation system is comprised of an intracortical array in M1, machine learning frameworks, and a stimulation device to evoke desired movements. In this study, we extend the capabilities of the BCI by decoding residual sensory signals from the array and using the outputs to control a vibrotactile device for artificial sensory feedback. We have demonstrated that robust time-locked neural activity in M1 is evoked by stimulation of residual somatosensory circuits on the arm and hand and can be reliably decoded. We further confirmed that during active object manipulation, afferent sensory signals are present in M1, can be decoded in real-time, and used to control a sensory feedback device for overcoming impaired hand sensory function. Using the closed-loop feedback system, the participant had enhanced object touch detection, sense of agency, movement speed, and other sensorimotor functions. The closed-loop sensory feedback system was able to detect residual sensory signals from up to the C8 spinal level. Overall, our results support the hypothesis that sub-perceptual neural signals can be decoded reliably and transformed to conscious perception, significantly augmenting sensorimotor function.

The work that we plan to present at this conference is in the process of being published in a peer-reviewed journal. We are currently performing additional assessments of the sensory signals recorded in motor cortex during complex object manipulation. In the short-term, we will improve our system's capabilities by integrating deep neural network decoding frameworks inspired by the architecture and function of the spinal cord, further replacing broken neural networks. We are currently aiming to utilize the decoded sensory signals for continuously modulating our muscle stimulation device and optimizing grip quality during object manipulation. Additionally, we are miniaturizing our current system to develop a completely portable reanimation system for SCI patients with tetraplegia. We are excited for the future of BCI technology that maximizes sensory and motor information extraction from ongoing brain activity for functional benefit.

*Internal funding from Battelle Memorial Institute & The Ohio State University*

## Poster #17: Manipulating biological clocks to improve post-SCI metabolic function

Andrew D. Gaudet, Sung-Hoon Park, Laura K. Fonken

University of Texas at Austin Department of Psychology; Department of Neurology

**Background:** Spinal cord injury (SCI) can disrupt metabolic function, predisposing individuals to cardiovascular disease and other health risks. Metabolic function is synchronized with the environment via the circadian system. We now know that SCI dysregulates both daily rhythms and metabolism; however, the link between the circadian clock and metabolic function is unclear. We hypothesize that SCI in rodents disrupts daily rhythms of key circadian factors - both in the spinal cord and in peripheral tissues - and that SCI-elicited circadian disruption contributes to metabolic dysfunction.

### **Project Goals:**

1. Determine whether SCI causes circadian disruption and related metabolic dysfunction.
2. Establish whether clock disruption further impairs post-SCI metabolic recovery.
3. Reveal whether boosting circadian rhythms improves post-SCI metabolic function.

**Research Methods:** *In vivo:* Mouse and rat models of SCI (moderate midline T9 contusion); locomotor behavior; new methods to assay sensory function; circadian behavioral outcomes; and metabolic measures. *In vitro:* Culture of various cell types; co-culture strategies; circadian outcomes using a *Per:Luc* system. Microscopy; flow cytometry; expression of genes/proteins; gene/protein pathway analysis.

**Project Status:** Our initial studies were completed in female and male rats. Compared with sham rats, SCI rats had several dysregulated “peripheral oscillators” - factors that entrain daily rhythms in peripheral cells of the body - including corticosterone, body temperature, and activity. These oscillators all gradually recovered more typical rhythms within 14 d post-injury. Further, SCI dysregulated circadian metabolic function, including ablated defecation rhythms and altered plasma glucose levels. In parallel, 2 d post-SCI rat livers showed altered expression of clock genes and glucose metabolism machinery genes. Together, these data suggest that moderate SCI causes widespread circadian disruption, that can gradually recover over time.

**Next steps:** Our results demonstrate that SCI has parallel disruptive effects on circadian rhythms and metabolic function; however, it remains unknown whether SCI-elicited circadian disruption causes the pathological metabolic changes that occur post-SCI. Upcoming studies in the Gaudet Lab will establish (1) whether global and/or liver-specific clock disruption further impairs post-SCI metabolic recovery; and (2) whether beneficial circadian interventions early post-SCI can improve post-SCI metabolic function.

**Poster #18: Texas A&M Spinal Cord Initiative (TAMSCI): Launching a multi-disciplinary center for research on spinal cord injury**

Cédric GEOFFROY, Jennifer DULIN, Hangu Park, Dylan McCREEDY, Michelle HOOK, Nicholas JEFFERY, Tim ELLIOTT, Jonathan LEVINE, Jim GRAU

*Texas A&M, Texas A&M Spinal Cord Initiative (TAMSCI)*

The Texas A&M Spinal Cord Initiative (**TAMSCI**) fosters research to discover new treatments to promote recovery after spinal cord injury (SCI). TAMSCI includes 9 highly-collaborative laboratories with unique areas of expertise and complementary technical approaches, including 4 new hires. All teams have a common goal toward facilitation of functional recovery, by increasing cell survival, promoting axon regeneration/remyelination, stem cell transplantation, reducing neuro-inflammation, promoting adaptive plasticity, and fostering rehabilitative care. Importantly, each laboratory brings unique and specialized understudied research interests that focus on “Non-Classical” consequences and health complications associated with SCI.

The 4 new hires include Jennifer Dulin, Cédric Geoffroy, Dylan McCreedy and Hangu Park. The **Dulin** laboratory focuses on optimizing neural progenitor cell transplantation to reconstruct neural circuits after SCI, with the goal of identifying the specific cellular components of cell grafts that are most potent for restoring sensory and motor function. The **Geoffroy** laboratory is assessing how SCI leads to liver pathologies, metabolic syndrome and cardiovascular complications. Geoffroy is also performing *in vivo* screen and gene therapy to better understand the age-dependent decline of axon growth. **Park** is investigating the effect of sensory augmentation on balance training in humans after incomplete SCI, and is interested in correcting swallowing dysfunction following cervical SCI. Collaborative work by Park and Hook is also examining how SCI affects somatosensory feedback in the rodent model. Park and Geoffroy are working to electrically stimulate the colon to reduce neurogenic bowel dysfunction. Hook, Geoffroy and Park are investigating the roles of age, inflammation and reduced neural innervation in the dramatic bone loss seen after SCI. The **McCreedy** laboratory investigates mechanisms of acute inflammatory damage including the role of immune cell adhesion receptors and signaling pathways that activate pathogenic effector functions. McCreedy is also developing tissue clearing and 3D lightsheet imaging techniques to visualize inflammation, tissue damage, and neural plasticity in whole cord.

The launch of TAMSCI is building upon existing strength at Texas A&M in the area of SCI. Indeed, the **Hook** laboratory has examined the consequences of opioids on functional recovery and has pioneered studies of addiction and depression in the rodent model. The **Grau** laboratory is examining the plastic potential of neurons within the spinal cord, demonstrating that these neurons can support simple forms of learning, and exploring how pain input after injury (polytrauma) affects recovery. The **Levine** laboratory is conducting genetic studies focused on recovery from naturally-occurring SCI in dogs. They also work on imaging features of injury, biomarkers, and perform clinical trials in dogs. **Jeffery** lab is studying bladder function and assessing the neutrophils functions and roles in the naturally-occurring dog SCI. The **Elliot** laboratory is studying well-being, including mental health and depression, of individuals living with SCI and their family caregivers.

**Poster #19: Disruption of a liver-spinal cord axis causes chronic liver pathology and systemic metabolic dysfunction after SCI.**

Matthew T. Goodus, Kaitlin E. Carson, Andrew D. Sauerbeck, Priyankar Dey, Richard S. Bruno, Phillip G. Popovich, Dana M. McTigue

Spinal cord injury (SCI) disrupts homeostatic control of organ systems at and below the level of the injury. This contributes to chronic systemic pathology, including hyperlipidemia, insulin resistance, high blood pressure and central adiposity. Collectively, these are symptoms of metabolic syndrome (MetS), which occurs at a higher rate in the SCI population. Consequently, people with SCI suffer from increased rates of cardiovascular disease, stroke and diabetes and increased morbidity and mortality. Since people are living longer after SCI due to improvements in acute care after injury, there is an urgent need to address these long-term issues of peripheral organ and metabolic health after SCI.

An organ central to metabolic homeostasis is the liver. We will present evidence showing that the liver is chronically and negatively impacted by SCI in rats in a way that mimics human MetS. Within days of mid-thoracic SCI and for at least 6 months post-injury, rodent livers display elevated pro-inflammatory cytokines and intraparenchymal macrophage accumulation and activation along excess lipid deposition compared to age-matched controls. This pathology is known as nonalcoholic steatohepatitis (NASH), which is the hepatic manifestation of MetS. SCI rodents also have elevated serum glucose, insulin, fatty acids and triglycerides, further verifying that SCI disrupts systemic metabolic control.

Current projects are working toward understanding how disruption of a liver-spinal cord axis drives hepatic pathology and metabolic dysfunction after injury. For this, we performed “gain of function” studies to enhance liver inflammation, such as bile-duct ligation or a high fat diet prior to SCI (which mimics the 30% of individuals who are obese at the time of their SCI), which reveal that if the liver is inflamed at the time of injury, metabolic outcomes and overall recovery from SCI is impaired. Conversely, “loss-of-function” experiments are selectively depleting Kupffer cells (liver macrophages) before SCI to test the effects of reducing liver inflammation on hepatic and intraspinal pathology after SCI. These data show that reducing hepatic inflammation at the time of injury improves metabolic indices after SCI.

Collectively, our work is focusing on an aspect of SCI that receives relatively little research attention but has significant clinical implications. Our studies are uncovering how SCI disrupts liver physiology leading to development of chronic NASH and MetS. Importantly, NASH can progress to irreversible liver cirrhosis, liver failure and hepatocarcinoma, which is 7x higher in SCI individuals compared to the general population. Because NASH can drive features of MetS, discovering treatments to resolve liver inflammation and fat accumulation will likely improve metabolic health in SCI individuals, and potentially reduce overall morbidity and elevated mortality in the SCI population.

## **Poster #20: Development of auto-positioning robotic systems which move devices to usable positions based on eye and face positioning or gestures**

Dianne Goodwin, Peter Loeffler, Marty Stone

*BlueSky Designs, Inc.*

**Project Goals:** The project goal is to increase independence and access for individuals with upper extremity limitations, reducing their reliance on others. The robotic positioning system automatically moves devices such as phones, tablets, eye-gaze systems, and drink/hydration tubes to usable positions. The robotic system can move automatically, according to a person's position, or be controlled by switches, voice, face or eye gestures.

**Research methods:** A multi-disciplinary team is involved in development and testing. Rehabilitation Engineers, Mechanical and Electronics Engineers and software developers design the technology. Consumers, family members and assistive technology professionals provide input, test prototypes and offer feedback.

Iterative development cycles include descriptions and flowcharts of how it works, electronic and mechanical prototype development, and testing by consumers and clinicians. Feedback is considered, revisions made, and the cycle continues.

Electronics development: Off-the-shelf development kits are used in electronics and firmware development. Computers analyze and compare inputs and outputs. Tools such as Altium are used to lay out printed circuit boards. A short run of boards is produced for testing of inputs, outputs, command processing, and power.

Mechanical design includes CAD development to design hardware and housings, and 3D printing to validate the design. Off-the-shelf components are purchased in small quantities.

App development begins with storyboarding, graphics development and Android and iOS coding. Testing: In-house testing for function, safety and usability is performed by project and non-technical staff. Once validated, prototypes are tested by clinical partners and consumers for functionality and usability.

**Current project status and short-term next steps :** The initial system used a simple logic and movement sequence to move the arm based on face position data. The system would keep following the person's face. We found it necessary to "pause" the system once it found a valid eye gaze use position. Otherwise, the system continued to move whenever the user moved their face.

The current system begins by looking for a face. It detects the face position data, compares it to known values for a good "use" position and then calculates where and how it needs to move. Its path is based on the differences between the two and logic defining a "keep out" zone. This version ran into trouble because the design did not allow multi-channel communications. Next steps include:

Electronics and firmware upgrades: We are in the process of updating components so the system can handle multiple channels of data, including computer vision camera, joint positions and switch input from an end user. Six prototype systems will be built for testing and development.

App development: The power mount app will be redesigned to add Auto-positioning features, including feedback during the "Find Me" phase, and user's use preferences.

User testing: Once the new system is functioning, user and practitioner testing will begin.

Future OpenCV work: At this time, either the built-in camera of an eye gaze system or an Omron development kit is used. Future development involves using OpenCV and a camera to develop an eye/face gesture switch.

*Funding source(s): NIH / NICHD Small Business Innovation Research program, ALS Challenge Grant*



## **Poster #21: Breathing easier after spinal cord injury: how apoE genotype modulates respiratory motor plasticity**

Lydia E. Hager, Kyle J. Ritter, Daimen R. Stoltz, Chris M. Calulot, Emily E. Huffman, Warren J. Alilain

*Spinal Cord and Brain Injury Research Center, Department of Neuroscience, University of Kentucky College of Medicine*

Each year, 17,700 Americans suffer a spinal cord injury, over half of which occur at the cervical level. These high level injuries can interrupt bulbospinal neurons that innervate the phrenic motor nucleus, the origin of the phrenic nerve. Loss of these descending inputs to the phrenic nerve paralyzes the ipsilateral diaphragm, leading to breathing impairments. One approach to promote recovery of breathing function is by enhancing plasticity through strengthening of synapses or activating spared but latent pathways in the spinal cord. Activation of the latent crossed phrenic pathway can lead to a form of respiratory motor plasticity known as long term facilitation (LTF), which is characterized by a prolonged increase in breathing motor output. LTF can be induced through exposure to intermittent hypoxia (IH) or by intermittently dosing the spinal cord with serotonin (5-HT). However, therapeutics designed to enhance plasticity have thus far met with varied success. When developing therapeutics in preclinical models, experimental groups are often homogenous, consisting of animals of the same strain and sex, which misrepresents the diversity of the human population. Just as people differ in traits such as hair color, height, and skin tone, genetic variability may also lead to differences in the capacity for neural plasticity. Apolipoprotein E (ApoE) is a promising candidate gene that could modulate plastic responses after injury. The E4 allele of apoE has previously been shown to reduce synaptic plasticity by decreasing surface expression of glutamate receptors when compared to the E2 or E3 alleles. The present study investigates the influence of human ApoE4 on respiratory motor plasticity in rats following C2 hemisection. 20 weeks after injury, rats were dosed with one isoform of the human ApoE protein, E3 or E4, prior to receiving intermittent 5-HT to induce LTF. Diaphragmatic EMG recordings demonstrated that animals exposed to human ApoE3 protein exhibited an increase in diaphragmatic activity ipsilateral to injury, but this increase was abolished in E4 dosed animals. To determine whether this decrease in respiratory motor plasticity is due to a difference in synaptic glutamate receptor expression, glutamate receptors localized to excitatory synapses were quantified and compared between genotypes. Data showed that apoE4 treated animals were unable to upregulate synaptic glutamate receptors in response to 5-HT. Collectively, these experiments demonstrate ApoE4's potential to inhibit plasticity following spinal cord injury, emphasizing the importance of considering genetic diversity while developing SCI therapeutics for the human population. Future directions for this project include measuring expression of molecules that are crucial for induction of LTF and comparing them between genotypes. Importantly, experiments will also be performed in targeted replacement mice that express the human apoE alleles in place of the murine form, which will provide a model that naturally expresses endogenous levels of apoE.

**Poster #22: Autonomic dysfunction after spinal cord injury**

Shaoping Hou, PhD, Assistant Professor (PI, Presenter)

Cameron T. Trueblood, PhD candidate

Jaclyn H. DeFinis, PhD candidate

Silvia Fernandes, PhD candidate

Jeremy Weinberger, MS, Research Assistant

Yuan Qiao, PhD candidate (Visiting student)

Shunyi Zhao, MS student

Alfredo Munoz, MD candidate (Part time)

*Spinal Cord Research Center, Department of Neurobiology & Anatomy, Drexel University College of Medicine*

Our research is aimed at understanding autonomic consequences after SCI, particularly lower urinary tract and cardiovascular disorders. We first elucidate spinal neuronal mechanisms regulating autonomic adaptation, and then employ multiple approaches, such as cell transplantation and axon regeneration, to reconstitute disrupted neuronal pathways for autonomic functional recovery. The Hou laboratory employs multidisciplinary approaches, including neuroanatomical, cellular and molecular, physiological, and behavioral techniques to elucidate supraspinal and intraspinal neuronal machinery of micturition and hemodynamics in both intact and spinal cord injured rat models. Utilizing the cell transplantation approach, our team attempts to rebuild neuronal pathways for autonomic functional recovery. In the central nervous system, injured axonal projections are particularly refractory to growth due to various factors. Thus, we are exploring effective strategies to reduce inhibitory aspects and increase growth capability for axon regeneration.

**Poster #23: V2a neurons promote recovery of breathing following spinal cord injury.**

Victoria N. Jensen<sup>1</sup>, Emily Huffman<sup>5</sup>, Warren Alilain<sup>5,6</sup>, Steven A. Crone<sup>1,2,3,4</sup>

1. *University of Cincinnati Neuroscience Graduate Program*
2. *University of Cincinnati Department of Neurosurgery*
3. *Cincinnati Children's Hospital Medical Center Division of Neurosurgery*
4. *Cincinnati Children's Hospital Medical Center Division of Developmental Biology*
5. *University of Kentucky Spinal Cord and Brain Injury Research Center*
6. *University of Kentucky Neuroscience*

Respiratory failure is the leading cause of death in spinal cord injury patients. Specifically, a high level spinal cord injury can paralyze the diaphragm, the main inspiratory muscle. We hypothesize that excitatory V2a neurons in the spinal cord and brainstem contribute to recovery of diaphragm function following injury. To test our hypothesis, we used a transgenic mouse line to activate V2a neurons after injection of the drug-like molecule clozapine-N-oxide (CNO). We performed a high level C2 hemisection (C2Hx) spinal cord injury to paralyze the ipsilateral diaphragm (same side as the injury) and measured muscle activity using electromyography (EMG) from the ipsilateral diaphragm to confirm paralysis. Increasing V2a neuron excitability with CNO restored rhythmic burst activity to the paralyzed diaphragm within hours or days after injury. Moreover, the contralateral diaphragm (uninjured side) is able to maintain regular rhythmic breathing when V2a neuron activity is altered. Finally, we show that silencing V2a neurons actually impairs the ability for nasal occlusion to restore bursting activity to the paralyzed diaphragm two weeks following injury. These results indicate that targeting V2a neurons has the potential to restore function to respiratory muscles following spinal cord injury without significant adverse side effects on respiratory rhythm generation. We next plan to 1) target only V2a neurons located in the cervical spinal cord near the site of injury to determine if this specific population of V2a neurons alone is also sufficient to restore activity to the paralyzed diaphragm and 2) determine if V2a neurons can restore breathing in a more clinically relevant contusion model of spinal cord injury.

**Poster #24: Review of evidence-based nutrition related strategies and research gaps to address while treating patients with spinal cord injuries**

Joetta M. Khan, PhD, RDN (1), Lara M. Mayoral, RDN (1), Veena K. Rajpal, MS, RDN, CNSC (1) Angie M. Ison, MS, RDN (2), Asma S. Bukhari, PhD, RDN (1)

(1) *Walter Reed National Military Medical Center, Bethesda, MD.*

(2) *Weed Community Hospital, Ft. Irwin, CA*

The incidence of spinal cord injuries (SCI) in the United States is estimated at 54 per one million people which is equal to about 17,700 new cases each year [1, 2]. The prevalence of individuals in the United States living with SCI is currently estimated to be about 288,000, majority of whom are male (78%) with leading causes including: vehicle accidents, falls, acts of violence and sports or recreation activity injuries, and approximately 51% were single at the time of injury [1, 2]. With advances in medical technology to treat SCI, the need to examine mechanisms to improve overall health outcomes and decrease long-term complications is imperative. Specifically, the role of nutrition in recovery phase and mitigate the development of chronic illnesses in individuals with SCI. The purpose of this review was to examine the state of the science (currently being studied, tested and shown to be effective in improving outcomes in patients with acute, sub-acute and chronic spinal cord injury) related to nutrition initiatives in patients with traumatic SCI relevant to the clinical practice guidelines that were last updated in 2009 [3]. A systematic literature review was conducted from May thru October 2018 by six registered dietitians serving as certified reviewers established through inter-rater reliability. An evaluation form and bias risk scoresheet was created based on PRISMA guidelines with a maximum bias score of 13 for the strongest study design. Articles were screened for inclusion, two independent reviewers evaluated each article, risk bias scores were calculated and all studies were presented and discussed at weekly meetings with all reviewers. Fifty-three articles (14% from initial literature review) were determined to meet the eligibility criteria and were included in this study. Areas of evaluation in the articles related to SCI and nutrition included (data presented as number of studies, mean±SD bias scores): dietary assessment (n=24, 6.29±2.64), nutrition screening tools (n=8, 5.62 ± 1.41), malnutrition (n=8, 5.25 ± 0.71), energy requirements (n=5, 3.8 ± 2.5), body composition (n= 43, 6.07 ± 2.60), biochemical analysis (n=24, 5.58 ± 2.13), dietary supplements (n=17, 7.22 ± 3.29), bone mineral density (n=5. 7.20 ± 2.77), and physical activity assessment (n=7, 5.28 ± 1.38). A key finding of this review is the lack of high quality nutrition-related research to provide necessary evidence to improve nutrition-related health outcomes in SCI population. Overall, a majority of the articles were of weak to moderate study design as indicated by low bias scores suggesting a need for future studies of stronger design to enable beneficial and more generalized conclusions to be drawn. These findings also indicate the need to integrate nutrition specific measures in other on-going larger scale SCI research protocols with strong study design to obtain high quality data. Sound research will enable development of evidence-based clinical practice guidelines across SCI continuum of care.

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## Poster #25: Development of a Stand Trainer for SCI Patients

Moiz Khan<sup>1</sup>, Isirame Omofuma<sup>1</sup>, Tatiana Luna<sup>1</sup>, Dario Martelli<sup>1</sup>, Enrico Rejc<sup>2</sup>, Joel Stein<sup>3</sup>, Susan Harkema<sup>2</sup>, Sunil K. Agrawal<sup>1,3</sup>

<sup>1</sup>*Department of Mechanical Engineering, Columbia University, New York, NY, 10027.*

<sup>2</sup>*Frazier Rehab Institute, University of Louisville, KY, 40202.*

<sup>3</sup>*Department of Rehabilitation and Regenerative Medicine, Columbia University, New York, NY 10032.*

The objective of this project is to improve the effectiveness of stand/balance training during rehabilitation of patients with spinal cord injury using a novel robotic device that supports a subject at the pelvis, trunk, and the knees. The stand trainer is designed to (i) provide active control of balance to the subjects during early training and controlled perturbations throughout training, (ii) quantitatively measure forces applied to the subjects at the pelvis and/or the trunk and measure their response of motion and/or ground reaction forces, (iii) free up multiple physical therapists from the labor intensive task of providing balance and support during training, and (iv) allow the clinical staff to concentrate on higher level aspects of the treatment session.

The stand trainer has a cable-based architecture and can apply external forces at three levels when a subject is standing, i.e., at the trunk, pelvis, and the knees. This system is controlled by 4 wires at the trunk, 8 wires at the pelvis, and 2 wires at the knees. Each wire is controlled by a DC motor and the controller uses the real-time data from a motion capture system for closed-loop control. Preliminary experiments were conducted on healthy subjects to test the capability of the system and examine the potential for robot-assisted stand training in the improvement of postural control in spinal cord injured individuals who are unable to stand independently.

Currently, we have created several algorithms for providing haptic feedback and assist-as-needed supportive forces. These include planar and 3D forcefields which provide assistance when the subject moves outside of their stability boundary in real time. In our recent work, we conducted experiments with healthy subjects to quantify human movements under different trunk and pelvis constraints and perturbations. Initial results show that a healthy subject can decrease postural variation during perturbations, when subjected to forcefield-based constraints. In the near future, we look to enroll incomplete SCI patients for characterizing their movement patterns in the standing position, while receiving assistive forces at trunk and/or pelvis.

## **Poster #26: A New Distributed Neuroprosthesis Enables Hand Grasp and Trunk Posture after Cervical Spinal Cord Injury**

Kevin L. Kilgore, Ph.D.; Harry A. Hoyen, M.D., Michael W. Keith, M.D.; Anne M. Bryden, OTR/L; Lisa Lombardo, PT, Ronald H. Hart, M.S.; Michael Miller, M.S.; Ronald J. Triolo, Ph.D.; Gilles C.J. Pinault, M.D.; Gregory A. Nemunaitis, M.D., Megan Moynahan, M.S., Kimberly D. Anderson-Erisman, Ph.D.; P. Hunter Peckham, Ph.D.

*MetroHealth Medical System, Case Western Reserve University, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH*

**Big Picture:** Our goal is to restore functional ability and independence for individuals with cervical level spinal cord injury (SCI) by providing functions such as hand grasp opening and closing, overhead reaching, trunk stability and standing.

**Research Methods:** Paralyzed muscles can be made to contract using electrical stimulation. By stimulating muscles in a coordinated fashion, it is possible to restore function to individuals with SCI. The user is given direct control of the movements by moving their remaining voluntary muscles (typically wrist extension and neck movements). We have developed a new modular implantable system, called the “networked neuroprosthesis” (NNP), which is capable of stimulating paralyzed muscles throughout the body and recording myoelectric signals from muscles under voluntary control. Using the NNP system, we can provide motor complete cervical SCI individuals with grasp opening and closing, overhead reach, and trunk stability.

**Current Project Status:** The NNP System has now been implanted in five individuals with SCI to date. The implementation of the NNP with each individual is customized to their retained function, but generally involves placement of 20-24 stimulating electrodes in the trunk and one upper extremity. Control is provided by 1-2 myoelectric signal recording electrodes in voluntary muscles in the forearm, shoulder, and neck. The implanted power module is placed in the abdomen. The results have been positive, and all subjects have demonstrated improved functional use of their hand and trunk. Demonstrated activities include eating with a fork, writing, and getting items out of the refrigerator. The NNP is the first modular neuroprosthesis designed to provide multiple coordinated functions for individuals with SCI. This system provides increased functional ability of the hand, arm, and trunk. The system is fully implanted (no external components), freeing the user in their activities.

**Next Steps:** Evaluation of all five subjects, as well as implantation of additional subjects, is ongoing. We are currently initiating a multi-center study of this system.

## Poster #27: Engagement in Community Activity after SCI: Evidence and Clinical Outcomes

B. Jenny Kiratli, PhD; Jeffrey Jaramillo, DPT; Jonathan Myers, PhD; Vandana Punj, MD; Doug Ota, MD

*Department of Veterans Affairs Rehabilitation Research and Development (RRD) Service; Department of Defense, Congressionally Directed Medical Research Program-Spinal Cord Injury Research Program (CDMRP-SCIRP) Spinal Cord Injury & Disorders Center, VA Palo Alto Health Care System*

**Big picture:** One of the primary objectives of rehabilitation after a spinal cord injury or diagnosis of spinal cord disorder is community integration. This includes social and physical engagement in recreation, work, school, etc. Much research has focused on barriers to community re-integration after discharge from rehabilitation, but less attention has been paid to those who are successful. We have recently completed a research study of consumer-defined realms of activity (beyond exercise or adapted sports) and identify the successful strategies persons with SCI/D use to achieve and maintain community activity. Our research investigations are highly integrated with clinical program initiatives to better understand the outcomes and therefore support community-based recreation and a broad range of activities for this population. Our approach is through partnership between clinicians, researchers, and consumers; this has allowed us to target significant problems and pursue clinically relevant avenues.

Past and current specific projects include a pilot case management approach to supporting community activity, in-home video gaming, community-based ballroom dancing, adaptive indoor rock climbing, and seated T'ai Chi; a future study is planned to employ virtual reality to support recreation exposure. The ultimate goal of our research program a continuum from research results to clinical implementation. Findings from the CDMRP-funded research project, "Successful strategies for wellness and activity after spinal cord injury" has provided key themes that can inform practices to encourage and support successful community integration.

**Methods:** We used a qualitative research approach in our CDMRP study of successful strategies. This included audio and video-recorded semi-structured interviews with consumers, family and support personnel, community coaches and facility staff, and clinicians. An interview guide was followed to explore pre-established topics while open-ended questions allowed a rich dialogue to develop leading to unpredicted findings and a more comprehensive representation of each person's experience than would have been possible with pre-selected surveys and structured queries. Analysis of these interviews used a serial review to identify key themes, initially based on pre-codes, and subsequently producing compiled and unique findings. This methodology allows each participant to provide personal evidence based on attitudes, beliefs, experiences as well as measurable information based on standard, validated surveys. One member of the research team was an individual with a SCI which provided an additional perspective both during execution of the study and interpretation of findings. In addition, we conducted physical and functional assessments and compared these quantitative data with our qualitative findings. Major results were that people with SCI defined activity very broadly, regardless of level of injury, and physical status was often not strongly associated with positive psychosocial benefits

**Next steps:** We plan to implement findings from this qualitative study into clinical practice to better define realms of community activity and thus capture meaningful outcomes. Implementation will include brief surveys of patient-defined activities and assessment of patient needs for support based on their identified goals. Lessons learned from the qualitative study will be applied towards supporting improved engagement in patient-identified activities.

## **Poster #28: Peripheral blood mononuclear cells compared to skeletal muscle to measure mitochondrial respiratory capacity after spinal cord injury**

Raymond E. Lai, Matthew E. Holman, Laura C. O'Brien, Qun Chen, Jeannie Rivers, Edward J. Lesnefsky, & Ashraf S. Gorgey

*Spinal Cord Injury and Disorders, Hunter Holmes McGuire VA Medical Center, Richmond, Virginia, USA.*

### **Introduction**

Skeletal muscle mitochondrial activity is decreased in type II diabetes mellitus, obesity, and after spinal cord injury (SCI) by up to 50-60%. This decrease in mitochondrial function may contribute to a higher incidence in obesity, type II diabetes mellitus, and cardiovascular disease in SCI. Muscle biopsies are currently obtained to assess respiration within mitochondria; however, this invasive procedure has risks and requires a team with specialized expertise. Alternatively, blood cells may also be predictive of mitochondrial health. **The purpose of the present study was to evaluate whether mitochondrial respiration of peripheral blood mononuclear cells (PBMCs) is predictive of respiration of permeabilized muscle fibers in individuals with SCI.**

### **Methods**

Fourteen SCI subjects between 18-65 years old with a BMI < 30 kg/m<sup>2</sup> were recruited to participate in the study as part of a clinical trial. Each was injured for ≥ one year and was classified using the American Spinal Injury Association impairment scale (AIS) as motor complete (A) or incomplete (B or C). Using high-resolution respirometry, mitochondrial respiratory capacity was measured for PBMCs and muscle fibers of the vastus lateralis. The function of individual electron transport chain complexes (complex I, II, and IV) were measured by the addition of substrates and inhibitors using a well-established protocol. Pearson's correlation coefficients and partial correlations were used to identify associations between PBMC mitochondrial activity and skeletal muscle biopsy mitochondrial activity. Bland-Altman analysis was used to determine the level of agreement between the Z-scores for the two methods. All values were reported as mean difference (95% CI) and statistical significance was accepted as  $\alpha < 0.05$ .

### **Results**

A significant positive correlation was observed between mitochondrial respiratory capacity of PBMC and permeabilized skeletal muscle for complexes II, IV, and I+II+IV ( $r = 0.610$ ,  $P = 0.027$ ; and  $0.842$ ,  $P < 0.001$ ;  $r = .89$ ,  $P < 0.001$ ; respectively). Conversely, no correlation was seen for complex I or I+II ( $r = 0.202$ ,  $P = 0.508$ ;  $r = 0.43$ ,  $P = 0.15$ ; respectively). Statistically significant relationships between PBMCs and permeabilized muscle fibers were maintained when controlling for age, weight, BMI, and time since injury in the partial correlation analyses. Bland-Altman plots for PBMCs and permeabilized muscles fibers displayed good agreement for complex II, IV, I+II, and I+II+IV with no significant biases ( $P > 0.05$ ).

### **Conclusion**

Primary findings suggest that respirometry measurements acquired from PBMCs may serve as a viable alternative for assessing mitochondrial respiration compared to skeletal muscle tissue. Future work should explore other minimally/noninvasive options including near-infrared spectroscopy for determining mitochondrial health after SCI. Additionally, we would like to investigate how different exercise paradigms may improve mitochondrial function within this population.

**Keywords:** PBMC, permeabilized skeletal muscle, spinal cord injury, mitochondria



## **Poster #29: Neuroprosthetic and Neurotherapeutic Interventions for Improving Personal Health, Mobility and Independence after SCI**

Lisa Lombardo, M.P.T.; Musa Audu, Ph.D.; Stephanie Bailey, B.S.; Kevin Foglylano, B.S.; Rudi Kobetic, M.S.; Nathan Makowski, Ph.D.; Mike Miller, M.S.; Gilles Pinault, M.D.; Stephen Selkirk, M.D./Ph.D.; Brooke Odle, Ph.D.; Ronald Triolo, Ph.D.

*Louis Stokes Cleveland VA Medical Center and Case Western Reserve University*

**Overview:** The overall mission of the Motion Study Laboratory (MSL) at the Louis Stokes Cleveland VA Medical Center and Case Western Reserve University is to enhance independent daily function, improve wheeled and personal mobility, expand home and community access, and promote the overall health and well-being of individuals paralyzed by spinal cord injuries, stroke or multiple sclerosis through neuroprostheses and other assistive technologies. Ongoing research projects utilize unique of laboratory capabilities in terms of biomechanical analysis and quantification of rehabilitation outcomes, neuroprosthetic/neurotherapeutic applications of peripheral nerve stimulation, and assessment of intervention effectiveness from the perspectives of the caregiver as well as the individual with SCI in home and community environments.

The MSL is a specialized rehabilitation and outcomes assessment facility dedicated to developing and quantifying the effects of new technical and clinical interventions to facilitate, enhance or restore neuromuscular function after paralysis. Exercise, recreation, and independent personal mobility (transfers, standing, walking and manual wheelchair propulsion) in the home and community are emphasized. Capabilities include: surface or implanted peripheral nerve stimulation; electrophysiological, metabolic and kinetic/kinematic measurement; dynamometry; quantitative gait and balance analysis; wireless/wearable sensing; simulated activities of daily living; bodyweight supported and virtual reality training and assessment; biomechanical modeling and control system design; and rehabilitation robotics.

**Methods:** Patterns of stimulation to achieve clinically useful movements are optimized based on able-bodied data, simulations, and user input prior to home and community use. Multicontact nerve cuffs access independent motor unit pools and multiple muscle targets. Activating hip and trunk muscles restores seated postures, maintains trunk stability, expands reachable workspace, and improves manual wheelchair propulsion. Coordination with knee and ankle muscles facilitates transfers, standing, stepping, and other functional activities. Wireless sensors update stimulation to respond automatically to destabilizing events or to generate fluid motions. Motorized exoskeletons are added to assist stepping or stairclimbing and ensure consistent walking distances and speeds appropriate for community ambulation. Surface stimulation is utilized for rehabilitation, exercise and recreational programs such as rowing and stationary/overground cycling to broaden applicability to wider SCI populations.

**Status:** Neuroprosthesis recipients with low-cervical or thoracic SCI can exercise, transfer, stand, and step after only weeks of reconditioning exercise and training. One hand can routinely be released from a walker, enabling users to reach and manipulate objects overhead. Advanced control systems automatically modulate stimulation to maintain balance and further reduce interactions with support devices. Hip and trunk stimulation normalizes vertebral alignment and pelvic tilt during quiet sitting, and returns users to erect postures from forward or laterally flexed positions, enabling bimanual reaching or retrieving objects from the floor. Stabilizing the torso with stimulation increases manual wheelchair propulsion efficiency, and prevents falls during sudden stops and turns. Wheelchair propulsion/stability systems are being prepared for home and community trials. Automatic control systems to set and maintain task specific sitting or standing postures are under development. Effort and safety of stimulation-assisted floor-to-wheelchair and sitting pivot transfers are being quantified from both user and personal assistant perspectives. Standing and rowing/cycling distances are being extended by alternating between non-overlapping motor unit pools to allow rest and recovery. Hybrid walking systems integrating muscle power with motorized exoskeletal assistance are ready for SCI testing, and over-ground cycling with surface stimulation is being prepared for implementation at collaborating sites.

**Plans:** Investigators continue to seek collaborative approaches to determining the physiological and psychosocial impact of new neuroprosthetic technologies and neurotherapeutic techniques that enhance the intrinsic enablement, health and well-being of persons with paralysis.

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## Poster #30: System-Wide Changes at a Single Cell Resolution: Profiling the Lumbar Cord following Thoracic Contusion

\*Kaya Matson<sup>1</sup>

Daniel Russ<sup>2</sup>, Ph.D.

Claudia Kathe<sup>3</sup>, Ph.D.

Anupama Sathyamurthy<sup>1</sup>, Ph.D.

Jordan Squair<sup>3</sup>, Ph.D.

Gregoire Courtine<sup>3</sup>, Ph.D.

Ariel J. Levine<sup>1</sup>, M.D., Ph.D.

<sup>1</sup> *National Institute for Neurological Disorders and Stroke*

<sup>2</sup> *National Institute on Deafness and Other Communication Disorders*

<sup>3</sup> *Center for Neuroprosthetics and Brain Mind Institute, Swiss Federal Institute of Technology (EPFL)*

Injury to the spinal cord elicits a wide range of biological changes, ultimately disrupting neural circuitry and resulting in paralysis. Given that the biological response to SCI is multi-faceted, with microglia, astrocytes, oligodendrocytes and a diverse array of neurons changing their molecular programs and cell states, effective treatments must take these complex changes into account. Each of these cell types has an individual molecular profile, consisting of the expression of hundreds to thousands of genes that endow its function. Probing a cell's gene expression allows for an understanding of its cell type and current state, including its cellular pathways, structural components, receptors, and ligands. However, current techniques limit our understanding of such a complex system. By studying the role of individual cell types, we are unable to understand the entire system, and by studying bulk changes in gene expression we cannot examine rare cell types or subpopulations. Recently, we adapted RNA sequencing with single cell resolution to profile every gene expressed in all the cell types in the lumbar spinal cord in an unbiased high-throughput manner. By profiling the nucleus from thousands of cells at once, we can study heterogeneous tissues such as the spinal cord at a system-wide level. This method avoids experimentally-induced gene expression and selective cell death common in single cell profiling, allowing for the study of vulnerable cell types such as motoneurons. Using the molecular profiles from over 17,000 nuclei, we identified major cell types including neurons, oligodendrocytes, astrocytes, and microglia, as well as 43 distinct neuronal populations in the adult mouse lumbar spinal cord. This work provided an unbiased characterization of neuronal populations, and serves as a resource for not only providing additional molecular markers, but also the ligands and signaling pathways that contribute to the molecular landscape of the cell. We have since further optimized this protocol to yield greater throughput per sample in a robust manner, opening the door to using more precious and variable samples such as diseased or injured spinal cord. With single cell resolution and massively parallel size, this will allow us to investigate the response of all cells, from major cell types to rare populations in the lumbar spinal cord following injury. Indeed, preliminary data on 70,000 nuclei from lumbar segments of intact and thoracically contused mouse spinal cords captures immense complexity of the molecular changes within and between cell types. Ongoing work includes validating findings and investigating exciting cell-type specific and between-cell molecular changes following SCI. This work enables the study of gene expression at both a cellular resolution and a system-wide perspective, thereby identifying network-level changes following SCI as well as potential targets for therapy and functional recovery in the lumbar spinal cord.

**Poster #31: Pathways to Field-Testing Clinical Guidelines: the 36 Billion Dollar Missing Link.**

Dr. Stephen McKenna<sup>1,5</sup>; Dr. James Crew<sup>1</sup>; Ben Dirlikov<sup>2</sup>; Dr. Reza Ehsanian<sup>3</sup>; Dr. Adam Ferguson<sup>4</sup>; Dr. Michael Beattie<sup>4</sup>; Dr. Graham Creasey<sup>5</sup>

*1 Dept of PM&R, Santa Clara Valley Medical Center; 2 Rehabilitation Research Center, Santa Clara Valley*

This effort began with a breakfast forum at the 2015 International Spinal Cord Injury Society (ISCoS) meeting in Montreal, Canada. The group was composed of leaders from funding agencies (NIH, national and international NGOs), Data Collection Centers (SCI Model System and European Multicenter Study about SCI), SCI leadership from ASIA and ISCoS. Over subsequent years, the focus of this effort has converged on a specific proof of concept utilizing a “big data” approach to Field-Test Clinical Guidelines. Specifically, Clinical Guidelines can be converted into clinical management algorithms (e.g. early blood pressure augmentation) and “natural history” experiments can be conducted comparing outcomes based on changes to practice (e.g. introduction of Spinal Cord Perfusion based augmentation) by comparing robust baseline data vs. post intervention outcomes (all data collected automatically within the existing EHR).

Current project status and short-term next steps (please avoid using technical jargon): Strategies to conduct these natural history experiments are already being discussed. This subject was the topic of the Anthony DiMarco lecture presented at ASCIP 2017 and a working group of clinicians presented a lecture on the feasibility of the approach at ASIA 2018. The Information

Technology departments of hospitals within our group have discussed the implementation of analysis of the entire EHR (radiological imaging, laboratory values, physiological parameters, medications, clinician notes, etc) for specific patients. The short-term next steps are to prioritize development of data pipelines which can act as the “Rosetta Stone” to support the effective Field-Testing of Clinical Guidelines in order to establish evidence-based practice algorithms. These data pipelines could then be used more broadly to accelerate research projects which were not previously feasible.

**Poster #32: NIH-Funded P2C Resource Center: The Alliance for Regenerative Rehabilitation Research & Training (AR<sup>3</sup>T)**

Laura Miller, PhD<sup>a</sup>; Michael Boninger, MD<sup>a</sup>; Linda Noble-Haeusslein, PhD<sup>b</sup>; Carmen Terzic, MD, PhD<sup>c</sup>; Thomas A Rando, MD, PhD<sup>d</sup>; Fabrisia Ambrosio, PhD, MPT<sup>a</sup>

*University of Pittsburgh<sup>a</sup>, University of Texas<sup>b</sup>, Mayo Clinic<sup>c</sup>, Stanford University<sup>d</sup>*

Cutting-edge technologies using biomaterials and cellular therapies to heal SCI are now entering clinical trials. The field of Regenerative Rehabilitation combines these discoveries with rehabilitation research to optimize outcomes. The Alliance for Regenerative Rehabilitation Research & Training (AR<sup>3</sup>T) is an NIH-funded national resource center that supports researchers and clinicians across the country, funding research, providing educational opportunities and propelling the translation of research findings into functionally relevant treatments, with the goal of transforming the future of healthcare.

In 2010, Dr. Michael Boninger and colleagues published a paper in the journal of *Physical Therapy* that emphasized the need for rehabilitation clinicians to work collaboratively with regenerative medicine researchers to optimize outcomes. This new field—Regenerative Rehabilitation—is based on research showing that electrical, thermal and mechanical stimulation affect the integration of regenerating stem cells and biomaterials in the body. The correct forces, timing of rehabilitation, and amount of stimulation are all critical factors that determine the success of treatment. NIH, recognizing the importance of this innovative direction, funded AR<sup>3</sup>T as a resource center to support awareness, understanding and growth of Regenerative Rehabilitation research and practice. An alliance of four institutions—the University of Pittsburgh, Stanford University, Mayo Clinic, and the University of Texas-- AR<sup>3</sup>T, with the resources of over twenty laboratories, is expanding scientific knowledge, expertise and methodologies across these two domains and accelerating the integration of regenerative medicine with rehabilitation protocols by providing support, education, training and funding opportunities. In addition, AR<sup>3</sup>T supports an annual international symposium on Regenerative Rehabilitation, the premier opportunity for thought leaders in rehabilitation as well as regenerative medicine fields to come together to learn about the latest developments, to share ideas, and to create sustainable collaborations in this new and cutting-edge field. AR<sup>3</sup>T is facilitating the translation of research findings from bench to bedside. Visit [www.ar3t.pitt.edu](http://www.ar3t.pitt.edu) to learn more about our resource center.

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### **Poster #33: The Enabling Mobility in the Community (EMC) Laboratory**

Kerri Morgan, PhD OTR/L ATP; Joseph W. Klaesner, PhD; W. Todd Cade, PhD, PT; Yan Yan, PhD; Kim Walker, OTD, OTR/L ATP; Sue Tucker, OTD, OTR/L ATP; Carla Walker, OTD, OTR/L ATP; Kelly Taylor, OTD, OTR/L; Lindsey Kampwerth, OTD, OTR/L ATP; Mike Scheller, PTA; Benny Chen, PhD Candidate; Trevor Thompson, OTD/S; Juli Harrison, OTD/S; Micki Lenderman, OTD/S; Carly Rusek, OTD/S; Courtney Weber, OTD/S; Brooke Evensen, MSOT/S; Emily Forsyth, OTD/S; Samantha Paton, MSOT/S; Anna Patten, MSOT/S

*Washington University Program in Occupational Therapy*

**Research Question or project goals:** The EMC lab conducts community-based research to bridge the gap between services offered to people with disabilities through rehabilitation and in the community. The overarching goal is to generate empirical knowledge helpful for guiding community-based interventions that improve the participation of persons with a spinal cord injury (SCI).

**Research methods or tools:** Strong methodological approaches are implemented to examine community-based interventions promoting health, decreasing secondary conditions, and improving physical fitness for people with disabilities that can be offered post-rehabilitation to enhance the participation of people with disabilities in meaningful life activities. The lab uses both quantitative and qualitative research approaches. Tools are used in the lab to measure health and participation (PROMIS measures), biomechanics (video motion capture system and a SmartWheel), and cardio metabolic health (blood tests, DEXA scans, and a metabolic cart). Implementation science methods are also used to help determine the feasibility of interventions in the community setting.

**Current project status and short-term next steps:** Pilot studies and feasibility studies are currently being conducted in the lab to explore: (1) development and testing of a computer-controlled roller for manual wheelchair users that can be used for exercise testing and/or wheelchair training; (2) development and testing protocols for cardiovascular fitness testing of persons with SCI who use manual wheelchairs; (3) examining (a) the number of task-specific repetitions required to produce change in wheelchair propulsion techniques and (b) the most conducive surface (overground or on a stationary device such as rollers) for implementing a repetition-based manual wheelchair propulsion training program; (4) examining the impact of a community-based exercise intervention for people with SCI on physiological and psychological well-being and identify barriers and facilitators to implementation; (5) determining the efficacy of high-intensity exercise protocols implemented on a wheelchair roller to improve cardiorespiratory fitness for persons with SCI who use a manual wheelchair; and (6) examining the trajectory of community participation over three years for persons aging with an SCI.

**Funding:** *Craig H. Neilsen Foundation; Missouri Spinal Cord Injury/Disease Research Program; National Institute on Disability, Independent Living, and Rehabilitation Research; National Institutes of Health; Encompass Health*

## **Poster #34: Overview of the Rehabilitation Engineering to Advance Ability Lab at VCU**

Carrie L. Peterson, PhD

*Virginia Commonwealth University, Department of Biomedical Engineering*

The goal of our research is to advance ability for individuals with neurologic deficits affecting their sensorimotor function. We advance ability by: 1) investigating the potential for neuromodulation to improve sensorimotor function, 2) elucidating the dynamics of functional tasks necessary for independent living, and 3) designing rehabilitation to optimize function. Our current projects aim to assess the potential for neuromodulation as an adjunct to physical training to improve upper limb function in individuals with cervical spinal cord injuries (SCI). We use non-invasive neural stimulation techniques to both assess and drive changes in neural function. Currently we test the reproducibility of cortical voluntary activation of muscle in individuals with SCI, and the potential of repetitive transcranial magnetic stimulation to increase corticomotor excitability of muscle in individuals with SCI. Elucidating the dynamics of functional tasks can help us to understand the movement forces acting on and within the musculoskeletal system. This research has many applications for rehabilitation design and development. Recently, we determined the effects of upper limb reconstruction on shoulder joint forces in individuals with tetraplegia to increase our understanding of factors that contribute to shoulder pain. Through collaboration with researchers at the University of Wisconsin-Milwaukee, we currently aim to elucidate shoulder loading across the lifespan in wheelchair users with SCI. Using an experimental and simulation approach, we aim to quantify the effect of variability in wheelchair propulsion dynamics on shoulder joint mechanics. The long-term goal of this research is to provide rationale for the development of rehabilitation guidelines and protocols that minimize the risk for developing shoulder pain in wheelchair users.

## Poster #35: The Use of Wearable Accelerometers to Improve Mobility Prognosis

Stephanie Rigot, DPT<sup>a</sup>; Michael Boninger, MD<sup>a,b,c</sup>; Rachel Hibbs, DPT<sup>b</sup>; Dan Ding, PhD<sup>a,c</sup>; Lynn Worobey, PhD, DPT, ATP<sup>a,b</sup>,

<sup>a</sup> *Departments of Bioengineering,* <sup>b</sup> *Physical Medicine and Rehabilitation,* and <sup>c</sup> *Rehabilitation Science and Technology, University of Pittsburgh*

After a spinal cord injury (SCI), returning to walking is one of the primary patient goals, but only 25 to 34% of people are expected to walk as a functional mode of mobility. Clinicians must quickly decide where to focus therapy time to maximize an individual's functional mobility by discharge: either towards walking or wheelchair interventions. Our recent work demonstrated individuals who received gait training, but primarily used a wheelchair one year after SCI received less transfer and wheeled mobility training and had lower measures of community participation than non-ambulatory individuals who never received gait training. In the context of decreasing inpatient rehabilitation length of stays, it is crucial that time in therapy be used efficiently to maximize function at discharge and avoid those long-term consequences.

Clinical prediction rules (CPRs) can assist clinicians in determining a mobility prognosis early in the inpatient rehabilitation stay. However, common rules that use strength, sensation, and age to predict independent ambulation can be inaccurate for individuals with moderate strength and sensory impairments. By measuring actual lower limb movement (LLM) using accelerometers worn on the wrist and ankles, we aim to capture a more sensitive measure of strength and sensation than traditional manual muscle strength or light touch sensation testing. This measure of LLM has not been reported in literature for the SCI population and provides a novel use of wearable technologies in the early prediction of mobility prognosis. Our preliminary analysis has shown promise for the association between LLM, strength, and ambulatory ability (as defined by gait speed, endurance, and the need for assistance/bracing). Using machine learning techniques, we are able to determine which factors have the strongest association with ambulatory ability, among LLM, subject demographics, clinical characteristics, and other covariates.

Our long-term goal is to improve CPRs that predict ambulatory ability acutely after SCI, thus enabling appropriately targeted functional mobility training. As a first step towards this goal, we are building a foundational knowledge of LLM and its relationship as a potential biomarker for ambulatory ability cross-sectionally among individuals with chronic SCI and known, diverse functional abilities. We are also exploring longitudinal LLM and ambulatory ability data for a population with acute SCI to evaluate changes in LLM over the first year post-injury and create a preliminary prediction model. This will provide new understanding into factors that predict mobility in individuals with SCI and provide understanding as to how these factors change acutely following injury. Further, we will gain insight to guide a future multisite longitudinal study that will assess a new, more effective CPR. This CPR will aid clinical decision-making for individuals with SCI by allowing for optimally targeted therapies to be employed throughout the rehabilitation continuum, thus improving long-term functional outcomes.

## Poster #36: Inactivity exacerbates central and peripheral pathologies after incomplete SCI

Sujata Saraswat-Ohri<sup>1,2\*</sup>, Cynthia Gomes<sup>3\*</sup>, Julia H. Chariker<sup>4,5\*</sup>, Michal Hetman<sup>1-3</sup>, Jeffrey C. Petruska<sup>1-3</sup>, Scott R. Whittemore<sup>1-3</sup>, Eric C. Rouchka<sup>5,6</sup>, David S.K. Magnuson<sup>1-3</sup> (\*equal contribution)

1. Kentucky Spinal Cord Injury Research Center, University of Louisville
2. Department of Neurological Surgery, University of Louisville
3. Department of Anatomical Sciences and Neurobiology, University of Louisville
4. Department of Neuroscience Training, University of Louisville
5. Kentucky Biomedical Research Infrastructure Network Bioinformatics Core, University of Louisville
6. Department of Computer Engineering and Computer Science, Speed School of Engineering

Spinal cord injury (SCI) creates a whole-body disease condition that is driven largely by CNS dysfunction and manifests into acute and chronic pathophysiological changes. With the loss of supraspinal descending control, sensory neurons exert a much larger influence over spinal function, making the status of the bi-directionally influential dorsal root ganglion (DRG) neurons of paramount importance. DRG neurons release neuropeptides both centrally and peripherally; afferent information is provided via their central axons and tissue/organ physiology is affected via their peripheral axons. After SCI, nociceptive DRG neurons sprout both centrally and peripherally and exhibit hypersensitivity and spontaneous activity. Axonal sprouting centrally correlates with the development of neuropathic pain and autonomic dysreflexia. These negative effects are further exacerbated by inactivity and inflammation that act as pathologic, positive feedback loops. There is an inverse relationship between exercise and below-lesion nociceptor (C-fiber) sprouting, and both nociceptor hypersensitivity and neuropathic pain appear to be modulated inversely by activity. Rodents exhibit significant levels of spontaneous in-cage activity that begins within days of an injury and increases to 50-60% of their pre-injury levels by 4 weeks. In addition, rats show significant levels of recovery even following severe contusion with <10% spared white matter at the epicenter. It has been proposed that spontaneous in-cage activity acts as a type of rehabilitative therapy. In contrast, most humans experience immediate, profound and persistent inactivity after the initial event of a severe, but incomplete, traumatic SCI. *The main goal of this research project is to define the role that activity/inactivity plays in functional recovery after incomplete contusive SCI, with the premise that nociceptor plasticity is a major pathophysiological mechanism regulating locomotor, sensory, hepatic, and cardiovascular function.*

*Approach/methods:* Female Sprague Dawley rats received either T10 or T2 severe contusions. Activity/inactivity was modulated by placing paired animals in tiny, standard or large cages. Overnight activity, monitored for each animal, varied from ~30 m/night for injured animals in the tiny cages to ~150 m/night for injured animals in the large cages. Some groups received applied exercise using stepping in shallow water, a dynamically hindlimb-loaded partial body weight supported model where the forelimbs provide propulsion, or swimming, which fully unloads the limbs. Assessments of cardiovascular function (high-resolution ultrasound of the heart, carotid and superior mesenteric arteries) and analysis of genome-wide transcriptomic data from DRGs (below the levels of injury), liver and soleus muscle from chronically T2-injured rats, ± exercise, housed in tiny cages showed enhanced recovery with activity/exercise. Ongoing work includes the validation and functional analysis of the RNAseq data and histological analysis of C-fiber sprouting in central (spinal cord) and peripheral (liver and soleus muscle) tissues.



## Poster #37: Improving Neurogenic Bladder and Quality of Life after Spinal Cord Injury using Electric Stimulation.

Argyrios Stampas, MD<sup>1</sup>; Kenneth Gustafson, PhD<sup>2</sup>, Radha Korupolu, MD<sup>1</sup>, Christopher Smith, MD<sup>3</sup>, Sheng Li, MD, PhD<sup>1</sup>

*1. Department of Physical Medicine and Rehabilitation, McGovern Medical School, The University of Texas Health Science Center at Houston, 2. Case Western Reserve University, Dept. of Bioengineering, 3. Baylor College of Medicine, Dept. of Urology*

**Big Picture:** Using electric stimulation to prevent unwanted bladder reflexes that develop after spinal cord injury (SCI) may generate multiple positive long-term outcomes, including: reducing lifelong problems related to neurogenic bladder, including autonomic dysreflexia (AD); decreasing the use of bladder medications that may be expensive and cause unwanted side-effects; and improving overall quality of life in spinal cord injury.

**Background:** More than 1 million people in the world are living with SCI with devastating functional impairments, including paralysis and bladder dysfunction. The current approach to bladder management in SCI focuses on safely emptying the bladder and preventing incontinence, but this does not alter the natural course of a worsening SCI bladder. Instead, this “wait and see” approach introduces bladder medications once leaking or bladder accidents arise. While the medications can help prevent bladder accidents, they do not correct the underlying problem. Often required in higher doses for patients with SCI than those without, the medications can also cause side-effects such as dry mouth, constipation, and sedation, resulting in poor satisfaction and non-compliance. Furthermore, problems in the bladder are the most frequent cause of AD, a life-threatening condition in SCI. The current approach is clearly not enough to prevent urinary problems, reduced quality of life, or risk of AD. Not surprisingly, improving bladder function is the number one priority of those living with SCI.

A different treatment option is therefore necessary – and a non-medication approach using electric stimulation is showing promise. By preventing nerve changes in the SCI bladder within days after injury, this approach may be able to alter the worsening that is ordinarily observed. Altering nerve function (neuromodulation) may be accomplished for the bladder by stimulating the tibial nerve using surface electrodes. Called transcutaneous tibial nerve stimulation (TTNS), this process requires only a common rehabilitation electric stimulation device. We propose that TTNS started shortly after SCI and continuously used at home will demonstrate improved bladder and quality of life measures at 1 year and beyond.

In the first human clinical trial of TTNS in acute SCI, two weeks of 30-minute electric stimulation sessions via sticky electrodes to the tibial nerve located by the ankle were able to prevent reduction in bladder capacity, compared to controls with sham stimulation. Also, spastic reflexes were greatly reduced in the TTNS group compared to the control group. Furthermore, blood pressure and electrocardiogram recordings in this clinical trial suggest that management of the bladder with TTNS can impact the nervous system in a way which may decrease episodes of AD.

**Current project status and next steps:** Currently, TTNS is being evaluated in chronic SCI with the device and instructions supplied for home use. Preliminary evidence suggests that the TTNS home protocol is easy to direct and perform. Use of bladder medications significantly reduced and anticholinergic side effects decreased, all without changes in bladder accidents or catheterization patterns. The next steps are to study the effects of TTNS on the bladder from acute SCI to home use with long-term outcomes at 1-year and beyond.

**Poster #38: Inflammation After Spinal Cord Injury; Not The Same For Everyone**

**Research Team:** Andrew N. Stewart; Timothy J. Kopper; Michael B. Orr; William M. Bailey; Katelyn E.

McFarlane; Bei Zhang, and John C. Gensel.

University of Kentucky College of Medicine; Department of Physiology; Spinal Cord and Brain Injury Research Center (SCoBIRC)

Spinal cord injury (SCI) triggers a protracted inflammatory response that both aids recovery but also contributes to progressive neurodegeneration. The focus of our lab is to distinguish between destructive and reparative components of inflammation with the goal of mitigating post-SCI damage and improving recovery. We examine how physiological variables such as sex, age, and injury biomechanics affect post-SCI inflammation and recovery. Specifically, we have identified dichotomous pain responses between males and females after SCI, age-dependent treatment efficacy with anti-inflammatory therapies, and unique inflammatory responses depending on injury biomechanics. We use the evolving SCI demographic, with changing incidences of injury among males and females, age, and type of injury, to inform our pre-clinical and basic science research. Our collective efforts aim to identify the extent to which tailored immunomodulatory therapies can improve both function and pain outcomes in a demographic-dependent manner following SCI.

Our lab works at the interface between immunology and neuroscience and has technical expertise in immune-phenotyping, *in vitro* experimentation, SCI modeling with appropriate motor and pain evaluations, proteomics, transcriptional analysis, and immunohistochemistry. Using these techniques we recently observed an age-dependent increase of reactive oxygen species (ROS) production by macrophages within the injured spinal cord. ROS play important roles in normal cell functions but also exacerbate tissue damage following SCI. This age-dependent up-regulation of ROS suggests that ROS-based therapies may be more efficacious with age, which we recently validated post-SCI in a mouse model. Moving forward we seek to further develop ROS based therapies to mitigate age-dependent secondary injury caused by macrophages, as well as better define the implications of increased ROS on the development of pain and inflammation following SCI.

## Poster #39: Medical Gas Therapy for SCI: Repair Targets Revealed by Inhalation Treatment of Safe Dose Carbon Monoxide

Teng, Y.D.<sup>1,2,3,^\*</sup>, Han, I.B.<sup>1,2,3,#</sup>, Zeng, Z.<sup>1,2,3,#</sup>, Wang L.<sup>1,2,3,#</sup>, Aljuboori, Z.<sup>1,2,3</sup>, Yu, D.<sup>1,2,3</sup>, Anderson, J.E.<sup>1,2,3</sup>, Ropper, A.E.<sup>1,2,3</sup>, Ifedigbo, E.<sup>4</sup>, Kim, S.W.<sup>1,2,5</sup>, Haragopal, H.<sup>1,2,3</sup>, Augustine M.K. Choi<sup>4</sup>, Zafonte, R.D.<sup>1</sup>

1. Department of Physical Medicine and Rehabilitation, Harvard Medical School/Spaulding Rehabilitation Hospital, Charlestown, MA

2. Department of Neurosurgery, Harvard Medical School/Brigham & Women's Hospital Boston, MA

3. Division of Spinal Cord Injury Research, VA Boston Healthcare System, Boston, MA

4. Division of Pulmonary and Critical Care Medicine, Harvard Medical School/Brigham & Women's Hospital Boston, MA (Current address: Weill Cornell Medicine, Cornell University, New York, NY)

5. Division of Periodontology, Harvard School of Dental Medicine, Boston, MA

<sup>^</sup>Presenter; <sup>\*</sup>Corresponding author; <sup>#</sup>Equal contribution author

**Project goals:** We aim to develop carbon monoxide (CO)-based medical gas treatments via inhalation or injection of CO-releasing molecules (CORM) for acute and chronic SCI to recover sensorimotor and autonomic functions. **Study design and methodology:** Preservation and reactivation of neural and neuromuscular networks are essential for restoring function after SCI. However, blood-spinal cord and blood-brain barriers (BSB and BBB: formed largely by cell membranes) and disruption of blood flow prevent conventional drugs from reaching injured tissues. As a gas neurotransmitter CO can cross BSB/BBB by dissolving in membrane lipids to broadly interact with SCI-affected neural and muscular cells. CO also has antioxidant and anti-inflammation effect when given in safe low doses. We thereby first investigated whether CO inhalation could rescue epicenter neurons and axons in a rat model of T9 compression injury. In a replication study, 500 ppm CO, the most potent dose identified, was administered starting 4 hours post injury (p.i.) for 2 hours and thereafter 1 hour inhalation per day over 11 consecutive days. The outcomes of locomotion, anti-inflammation and neuromuscular protection were evaluated. In addition, the effect of CO on proliferation and development of adult neural stem cells (NSCs) in the lesioned spinal cord was examined to test our hypothesis that CO might stimulate NSCs via activating neurogenic signaling pathways. **Results:** CO treatment dose-dependently improved hindlimb function through sparing neural tissue and neuromuscular junction, resulting from reducing secondary inflammatory and oxidative damages. There were CO-increased NSC proliferation and trophic factor production in lower thoracic and lumbar spinal cord, compared to the control group treated with room air. The activation of NSCs lasted for 5-6 weeks after CO treatment (7-8 weeks p.i.), which appeared to be triggered by HO1-p38 MAPK-VEGF and p-nNOS signaling. Notably, the quantities of CO-mediated preservation of GABAergic and cholinergic interneurons in the spinal cord were positively correlated with the levels of hindlimb locomotor restoration. Developing neurons and serotonergic reinnervation were found in the interneuron zone and lumbar segment, respectively, of CO-treated spinal cords. Taken together, the data suggested that safe dose CO inhalation improved hindlimb function in rats with acute T9 SCI by preserving neural and neuromuscular networks. Moreover, CO may be devised into a therapy to manage inflammatory complications (e.g., neuropathic pain) and reduce disability for chronic SCI via augmenting endogenous NSC-triggered neuroplasticity. **Current project status and short-term next steps:** We are verifying the involvement of the proprioceptive system in facilitating the therapeutic impact of CO and in the process of getting the findings published. Our ongoing tasks are designing and organizing studies to investigate the effect of CORM following intrathecal injection on neural repair and functional recovery after SCI.

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## Poster #40: Operant conditioning of the Motor Evoked Potentials to Enhance Motor Function Recovery Team

Aiko K. Thompson (National Center of Neuromodulation for Rehabilitation (NM4R), Medical University of South Carolina (MUSC)), Christina Gill (NM4R, MUSC), Bridgette Pouliot (NM4R, MUSC), Michelle Woodbury (NM4R, MUSC), Richard Segal (NM4R, MUSC), Jonathan Wolpaw (National Center for Adaptive Neurotechnologies, Wadsworth Center, NY State Department of Health), Monica Perez (University of Miami)

After spinal cord injury (SCI) corticospinal excitability diminishes, resulting in weak voluntary activation of muscles and impaired motor control. Such deficits are partially reversible; corticospinal excitability increases in association with motor function recovery. Thus, an intervention that further improves corticospinal excitability may enhance motor recovery. While several new methods targeting corticospinal tract are currently being developed (e.g., Neurotherapeutics. 2018;15:618-27; Clin Neurophysiol. 2016;127:724-31), their long-term impact is yet to be determined. At present, no interventions/therapies that aim to restore corticospinal excitability are readily available to people with SCI. Operant conditioning of a stimulus-triggered EMG response, which can target beneficial plasticity to the pathway that produces the response (Prog Brain Res. 2015;218:157-72), may be able to fill this gap. **The overarching hypothesis of this project is that increasing the size of the motor evoked potential (MEP) to transcranial magnetic stimulation (TMS) through operant conditioning can improve corticospinal activation of the targeted muscle and thereby improve motor function in which that muscle participates.** To test this hypothesis, and to investigate how MEP conditioning may be used to enhance motor function recovery, we are working on three projects.

### 1. MEP conditioning in lower extremity

Our initial hypothesis is that increasing the ankle dorsiflexor tibialis anterior (TA) MEP size through operant up-conditioning induces cortical and corticospinal plasticity that affects TA activation and improves locomotor EMG activity. Recently we completed initial studies of TA MEP conditioning, and found that people with or without chronic incomplete SCI can increase MEP size through operant up-conditioning (J Neurophysiol. 2018: Epub). Furthermore, this can improve locomotion in people with SCI (J Neurophysiol. 2019: Epub). Based on these findings, the current aims are to characterize (1) the cortical and corticospinal mechanisms of the TA MEP changes and (2) changes in locomotor EMG activity and on kinematics in people with SCI.

### 2. MEP conditioning in upper extremity

Our initial hypothesis is that the corticospinal excitability for the forearm extensors can be increased through MEP conditioning and that this will help to improve forearm motor function. Immediate aims are to investigate (1) whether the wrist extensor flexor carpi radialis and the finger extensor digitorum MEPs can be increased through up-conditioning in people with chronic incomplete cervical SCI, and (2) whether successful MEP conditioning can improve forearm motor function, such as reaching and grasping, and grooming.

### 3. MEP conditioning + motor practice to enhance function recovery

Our initial hypothesis is that in people with chronic incomplete SCI the TA MEP conditioning-induced plasticity and gait improvements can be enhanced by walking practice (3x160 steps or 3x5 min of moderate overground walking) that immediately follows conditioning.

General methods: The standard MEP conditioning protocol consists of 6 baseline and 24 conditioning sessions (at 3/week pace). Before and after MEP conditioning (or conditioning + motor practice), electrophysiological, kinematic, and functional assessments are performed. In each session, about 250 single-pulse MEPs are elicited over 30-45 min with or without operant up-conditioning (i.e., feedback on performance and encouragement).

**Poster #41: Dignify Therapeutics: Discovery and Clinical Development of Drug and Device Therapies for Bladder and Bowel Dysfunction following Spinal Cord Injury (SCI)**

Karl B. Thor, Ed Burgard, Mary A. Katofiasc, Lesley Marson, Daniel Ricca, Nadia M. Rupniak

*Dignify Therapeutics, LLC; Research Triangle Park, NC*

**Abstract:** SCI disrupts the brain's ability to voluntarily control micturition and defecation, resulting in urinary and fecal incontinence when storage is desired and urinary retention and constipation when voiding is desired. Management of bladder dysfunction involves bladder catheterization which can cause recurrent urinary tract infections, whereas bowel dysfunction is managed by bowel programs and digital stool extraction which are extremely time-consuming and stigmatizing for individuals and caregivers. In addition, these bladder and bowel care-methods can result in episodes of hypertension and bradycardia (autonomic dysreflexia) that is uncomfortable at best and can be serious.

The Dignify team, composed of internationally-recognized experts in research, discovery, and clinical development of novel therapies (primarily in urology and neurology), is specifically focused on research, discovery, and clinical development of drugs and/or devices that can restore voluntary control of micturition and defecation and eliminate or reduce urinary and fecal incontinence in individuals with SCI.

Dignify uses a "repositioning strategy", which uses previously discovered drugs/ targets that were proven safe in clinical trials when used for other therapeutic indications. Dignify then examines the effects of those targets? drugs on bladder and bowel function using in vitro and in vivo techniques to determine if there are potentially unrecognized benefits for their use as bladder and bowel therapies. Similarly, Dignify examines implantable neurostimulation devices, which were proven safe for clinical use in other indications, and then examines the ability of those devices to modulate nerve activity that controls micturition and defecation.

Our lead program involves the use of prokinetic drugs to provide an "on-demand, rapid-onset, short-duration, drug-induced voiding" therapy (publications listed below). These drugs have been shown to reliably induce highly efficient micturition and defecation in various animal species, including rats with chronic spinal cord injury, within minutes of administration. Because the drugs are small peptides, they are rapidly metabolized minutes after micturition and defecation are complete. Our 2<sup>nd</sup> program evaluates and repositions existing drugs that can provide "drug-facilitated" micturition for those individuals who can initiate micturition, but the voiding is incomplete (i.e. Underactive Bladder). Our 3<sup>rd</sup> program targets drugs that selectively provide drug-induced defecation to eliminate manual bowel programs. Our 4<sup>th</sup> program explores the use of a device to prevent urinary and fecal incontinence and prevent bladder-sphincter dyssynergia. Our 5<sup>th</sup> program is aimed at repositioning drugs to prevent autonomic dysreflexia.

*Dignify appreciates support from the NICHD, NIDDK, NINDS, and NIA for our lead program, which has resulted in the following publications:*

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DOI: [10.1124/jpet.118.248765](https://doi.org/10.1124/jpet.118.248765) DOI: [10.1007/s00210-017-1458-0](https://doi.org/10.1007/s00210-017-1458-0)

DOI: [10.1016/j.ejphar.2017.12.017](https://doi.org/10.1016/j.ejphar.2017.12.017) DOI: [10.1007/s00210-016-1317-4](https://doi.org/10.1007/s00210-016-1317-4)

DOI: [10.1016/j.ijpharm.2017.11.036](https://doi.org/10.1016/j.ijpharm.2017.11.036)

## Poster #42: Ischemic Spinal cord injury and paralysis after aortic aneurysm surgical repair

Esmerina Tili<sup>1,2</sup> MSc, PhD, (presenter), Gerard Nuovo<sup>3</sup> MD, Hesham Kelani<sup>1</sup> MD, Hossam Elsayed<sup>4</sup> MD, PhD, Ehab Ramadan<sup>1</sup> MD, Sarah Moore<sup>5</sup> DVM, Eric Bourekas<sup>6</sup> MD, Raphael Malbrue<sup>7</sup> DVM, MS, Mostafa Eltogby<sup>1</sup> MD, Michele D Basso<sup>8</sup> Ed.D, PT, Katherine Binzel<sup>6</sup> PhD, Michael Knopp<sup>6</sup> MD, PhD, Jean-Jacques Michaille<sup>2,9</sup> PhD, Hamdy Awad<sup>1</sup> MD.

<sup>1</sup>*Department of Anesthesiology, Wexner Medical Center, College of Medicine, The Ohio State University, Columbus, OH 43210.*

<sup>2</sup>*Department of Cancer Biology and Genetics, Wexner Medical Center The Ohio State University*

<sup>3</sup>*GNOME Dx, 1476 Manning Pkwy, Powell, OH 43065.*

<sup>4</sup>*Department of Surgery, Wexner Medical Center, College of Medicine, The Ohio State University*

<sup>5</sup>*Department of Veterinary Clinical Sciences, The Ohio State University*

<sup>6</sup>*Department of Radiology, Wexner Medical Center, The Ohio State University*

<sup>7</sup>*The Ohio State College of Veterinary Medicine, Columbus, OH 43210.*

<sup>8</sup>*School of Health & Rehabilitation Sciences, The Ohio State University*

<sup>9</sup>*BioPerox-IL, UB-INSERM IFR #100, Université de Bourgogne, Faculté Gabriel, 6 Bd. Gabriel, 21000 Dijon, France.*

Aortic aneurysms are surgically repaired either through open-chest or endovascular aortic stenting. Both, stenting, the mainstay of aneurysms repairs, and open repair carry comparable risks of ischemic spinal cord (SC) injury and paralysis. The non-invasive stenting therapy increased the number of patients who are offered therapy, but it also increased the number of paralyzed patients. In open repair the blood supply is disrupted and then restored therefore the injury to the SC is the result of both ischemia and reperfusion. In aortic stenting repair, the occlusion of intercostal arteries by the stents causes critical SC hypoperfusion without reperfusion injury.

To study the cellular and molecular mechanisms of SC damage after each type of surgery that would facilitate the design of future therapeutics, we have developed small and large animal models of both open and endovascular repair. In addition, we are also collecting blood and cerebrospinal fluid from both groups of patients undergoing aortic repair, with and without paralysis. We are using animal behavior assessment, imaging, histopathology, mouse genetics, cellular and molecular biology techniques to identify and validate future therapeutic targets for SC injury after each type of aortic surgical repair.

In mice and canines, temporary clamping of the descending thoracic aorta causes severe hindlimb spastic paralysis. The damage from open repair in both species, initiates in the SC gray matter, and is coupled with neuro-inflammation and vascular leakage. SC white matter is spared in open repair. We have established the pro-inflammatory microRNA *miR-155* to be a critical factor in this type of paralysis. As little is known about the cellular and molecular mechanisms contributing to aortic stenting-induced paralysis due to the lack of animal models, we developed a canine model of endovascular repair and are in the process of establishing the corresponding mouse model. In canines, endografted aortic stents (GORE®) occlude thoracic and lumbar intercostal arteries. In mouse, four pairs of thoracic intercostal arteries are being permanently ligated. Histopathology and imaging show that in contrast to the open repair, the SC damage after aortic stenting is primarily located within the white matter region, affecting axons and myelin, with relative sparing of the neuronal cell bodies in the gray matter. The manifestation of the injury in the white matter is mainly by axonal pyroptosis and massive myelin loss. In conclusion, our data show that ischemic SC injuries after open vs. endovascular repair are two distinct pathologies that require separate treatments and consideration.

### Poster #43: Standardizing Outcomes Measurement in Spinal Cord Injury Medicine to Advance Clinical Care

David Tulskey, PhD<sup>1,2</sup>

Pam Kisala, MA<sup>1</sup>

Callie Tyner, PhD<sup>1</sup>

Aaron Boulton, PhD<sup>1</sup>

Jerry Slotkin, PhD<sup>1</sup>

<sup>1</sup>University of Delaware Center for Health Assessment Research & Translation, Newark, DE

<sup>2</sup>University of Delaware Departments of Physical Therapy and Psychological & Brain Sciences, Newark, DE

**GOALS:** The goal of this research is to transform spinal cord injury (SCI) medicine to include routine evaluation of physical, functional, social, and emotional symptoms from the patient's perspective and to monitor people long-term to look for changes in these areas of functioning. This research will leverage a decade's work developing SCI-specific assessment tools, to translate this research into clinical practice through research on symptom clusters (i.e., clinical phenotyping), symptom identification and prevention, and self-management interventions. Additionally, this research focuses on standardizing assessment accommodations for individuals with the most severe disabilities.

**METHODS:** This research involves qualitative and quantitative methods, including focus groups and individual interviews, new survey research and reanalysis of previous data sets using advanced statistical techniques. One specific aim is to use cluster analysis to develop clinical groupings (or "phenotypes") of SCI symptoms and function that represent condition-specific and cross-condition disability classifications. Another specific aim is to develop self-management videos triggered by assessment scores.

**STATUS:** To date, we have created a comprehensive measurement system (SCI-QOL) designed specifically for individuals with SCI that evaluates a wide variety of important symptoms in physical (bowel, bladder, pressure ulcers), functional (mobility, fine motor, self-care), emotional (grief & loss, resilience, stigma), and social domains (ability to participate, independence). These have been closely linked with existing NIH measurement initiatives concerning other conditions (e.g., Neuro-QOL), generic health measures (e.g., PROMIS<sup>®</sup>), or standardized assessments (e.g., NIH Toolbox). The measures have been developed with extensive feedback from individuals with SCI and use innovative methods, including item response theory and computer adaptive testing. Unfortunately, SCI medicine lags behind other specialties that have integrated standard outcomes measurement into clinical practice. These measures can be used to monitor symptoms, improve patient-provider communication, and help providers tailor treatments to each patient. Next steps for this research are, therefore, to work on integrating these measures into electronic medical record platforms, such as EPIC<sup>®</sup>, to integrate into clinical care, and to track symptoms over time. Work is currently underway to develop clinically relevant cut scores and interpretive guidelines, including domain and global composite scores. A new "iManage-SCI" system for self-guided symptom monitoring and self-management is in the final stages of development, with a pilot study planned for 2019. The long-term goal of this research is to leverage modern measurement techniques to improve assessment, prevention, and treatment of physical, functional, social, and emotional symptoms and functioning following SCI.

#### **Poster #44: Autonomic Cardiovascular Dysfunction in SCI: Consequences, Assessment, Treatment**

Jill Maria Wecht, Caitlyn Katzelnick, Alexander Lombard, Matthew Maher, Meghana Noonavath, Gail Forrest, Ona Bloom, Nancy Chiaravalloti, Ann Spungen, Glenn Wylie, Susan Harkema, Noelle Carlozzi, Michael Kallen, Noam Harel, James Guest, William Bauman, Thomas Bryce, Miguel Escalon, Vincent Huang, Steve Kirshblum, Trevor Dyson-Hudson

*James J Peters VA Medical Center, Icahn School of Medicine, Mount Sinai, Bronx Veterans Medical Research Foundation, Kessler Institute for Rehabilitation, Kessler Foundation, University of Louisville, Frazier Rehabilitation, The Miami Project to Cure Paralysis, Feinstein Institute for Medical Research, Zucker School of Medicine, Northwell Health, Northwestern University, University of Michigan*

The impact of Spinal Cord Injury (SCI) on autonomic regulation of the cardiovascular system is not well understood and the degree of autonomic nervous system impairment is not easily assessed. Therefore, we seek to determine the effect of autonomic dysfunction on organ system function and my laboratory has been studying blood pressure control mechanisms in persons with chronic SCI for more than a decade. We have found that blood pressure abnormalities are common among individuals with SCI; however, clinical appreciation is lacking and upwards of 70% of the SCI population has some degree of blood pressure dysregulation while less than 1% is diagnosed or treated for these conditions. A primary goal of my laboratory is to raise awareness of the discrepancy between the incidence of hypotension and orthostatic hypotension and their diagnoses and we have sought to describe the impact of hypotension and orthostatic hypotension on cognitive function and quality of life in persons with SCI. We were one of the first laboratories to document deficits in memory and information processing in hypotensive individuals with SCI compared to a normotensive SCI cohort and believe that these cognitive deficits, may stem in part from dysregulation of cerebral blood flow. We reported significantly lower blood flow velocities (suggesting reduced cerebral blood flow) in the middle cerebral artery in individuals with chronic SCI compared to age-matched controls. In addition, we found that both systolic blood pressure and diastolic flow velocity in the middle cerebral artery contribute to test performance on an information processing task and that relatively young (~34 years) individuals with SCI perform significantly more poorly than age-matched controls, but scores were comparable to an older (~55 years) nonSCI cohort. Premature cardiovascular aging has been suggested in the SCI population, our data support this and suggest that advanced cognitive aging may result from systemic and cerebral hemodynamic instability. However, clinical intervention to stabilize systolic blood pressure within normal limits i.e., 105-125 mmHg, and improve cerebral blood flow and cognitive function are not readily available and in fact there are few medications that have been proven safe and effective for widespread use in the SCI population to treat hypotension and orthostatic hypotension, as such many individuals remain untreated. We continue to explore associations between blood pressure, cerebral blood flow and cognitive performance in individuals with SCI and are determined to identify therapeutic treatment options that safely and effectively improve this paradigm. In addition, although most individuals with SCI remain asymptomatic, most anti-hypotensive agents have been approved by the FDA for the indication of dizziness while standing, and we are actively investigating the effect of treating low blood pressure, independent of symptoms, compared to treating symptomatic hypotension, as per usual clinical care, during acute rehabilitation after SCI, on time spent in prescribed physical therapy and on cerebral blood flow velocity. The focus of my investigatory work will continue to pursue rigorous trials aimed at lessening the impact of autonomic dysfunction on physiological, cognitive and psychological well-being to improve long-term health outcomes for veterans and non-veterans with SCI.



**Poster #45: Target  $\alpha$ -tubulin acetylation to promote neurite outgrowth and functional recovery after injury.**

Victor S.C. Wong<sup>1</sup>, Cristina Picci<sup>2</sup>, Michelle Swift<sup>3</sup>, Max Levinson<sup>4</sup>, Anthony Sauve<sup>5</sup>, Brett Langley<sup>2</sup>, Dianna Willis<sup>1,5</sup>

1. Burke Neurological Institute, 2. University of Waikato, 3. Drexel University, 4. New York University, 5. Weill Cornell Medicine

**Abstract:** Damage to the central nervous system (CNS), such as spinal cord injury, results in neuronal and axonal degeneration and subsequent neurological dysfunction. Endogenous repair in the CNS is impeded by inhibitory cues, such as chondroitin sulfate proteoglycans (CSPGs) and myelin-associated glycoprotein (MAG), which prevent axon regeneration. Previously, it has been demonstrated that the inhibition of histone deacetylase-6 (HDAC6) can promote microtubule  $\alpha$ -tubulin acetylation and restore the growth of CSPGs- and MAG-inhibited neurites. Since the acetylation of  $\alpha$ -tubulin is regulated by two opposing enzymes, HDAC6 (deacetylation) and  $\alpha$ -tubulin acetyltransferase-1 ( $\alpha$ TAT1; acetylation), we investigated the regulation of these enzymes downstream of a growth inhibitory signal. We used dissociated mouse cortical neurons incubated with CSPGs or MAG for various indicated times. We examined changes in tubulin acetylation levels, HDAC6 and  $\alpha$ TAT1 expression, and neurite growth using molecular and imaging techniques. Our findings show that exposure of neurons to soluble CSPGs and MAG substrates cause an acute and RhoA-kinase-dependent reduction in  $\alpha$ -tubulin acetylation and  $\alpha$ TAT1 protein levels, without changes to either HDAC6 levels or HDAC6 activity. The CSPGs- and MAG-induced reduction in  $\alpha$ TAT1 occurs primarily in the distal and middle regions of neurites and reconstitution of  $\alpha$ TAT1, either by Rho-associated kinase (ROCK) inhibition or lentiviral-mediated  $\alpha$ TAT1 overexpression, can restore neurite growth. Lastly, we demonstrate that CSPGs and MAG signaling decreases  $\alpha$ TAT1 levels post-transcriptionally via a ROCK-dependent increase in  $\alpha$ TAT1 protein turnover. Together, these findings define  $\alpha$ TAT1 as a novel potential therapeutic target for ameliorating CNS injury characterized by growth inhibitory substrates that are prohibitive to axonal regeneration. This study represents a paradigm shift as TAT1 provides a new target to promote axonal regrowth, in addition to HDAC6, which has received considerably more attention. Our immediate future plan is to complement these findings *in vitro* to *in vivo* setting using transgenic (namely HDAC6 and TAT1) knockout mice with spinal cord injury. Moreover, we are currently conducting a high throughput drug screen to discover compounds that can promote  $\alpha$ -tubulin acetylation in neurons *in vitro*. We will perform *in vivo* dosing studies of candidate compounds in spinal cord injured animals and examine their potential for functional recovery.

## Poster #46: Overview of the Mayo Clinic Spinal Cord Injury Research Program

Director: Kristin D. Zhao, *Mayo Clinic Rehabilitation Medicine Research Center*

The Spinal Cord Injury (SCI) Research Program resides within the Rehabilitation Medicine Research Center in the Department of Physical Medicine & Rehabilitation at Mayo Clinic Rochester. The Program is comprised of researchers and clinicians who span the translational biomedical research continuum from cellular-level regenerative research to patient-based health and wellness research, as well as clinical trials of emerging therapies.

The development and validation of novel strategies to improve and maintain health and wellness is an important research area for those living with SCI-related dysfunction. This is especially true for those seeking enrollment in clinical trials that require a history of stable health. Our team is interested in forging new directions in health, wellness, and novel therapies to improve the lives of individuals with paralysis by both maximizing retained functions, and recovering lost functions.

The SCI Research Program was formed to meet the needs of both patients with SCI, as well as researchers and clinicians from a variety of disciplines. Due to relatively recent advances in research, patients who seek research opportunities to improve lost function after SCI are contacting their physicians and medical care providers at increasing rates to inquire about these opportunities. Likewise, with new technological tools advancing research at a staggering rate, researchers desire a platform from which they can better communicate, collaborate and translate science between disciplines and across the spectrum from basic science discoveries, to clinically-oriented research.

The Program's mission is to foster collaboration in order to exchange of ideas, as well as raise awareness and financial support for SCI research at Mayo. Our program meets this mission by fostering multi-disciplinary, multi-institutional, and multi-departmental research. Monthly seminars bring clinicians and investigators together to share information about current clinical programs and research, as well as discuss gaps in practice and data fostering future collaborations. Research opportunities are shared with the patient population through medical providers, and as well as through internet presence, including social media.

Research is ongoing in the following areas, with dynamic interplay between them allowing novel directions and insights:

- Preventing and treating secondary complications of spinal cord injury, such as chronic shoulder pain due and pressure ulcers due to improper ergonomics or overuse while performing activities of daily living.
- Designing and implementing programs to enhance health, wellness and quality of life. These programs include virtual (i.e. online) resources, nutritional assistance, exercise, and performance metrics.
- Investigating cutting-edge approaches to recover functions lost due to spinal cord injury, such as epidural stimulation or lower-extremity exoskeletons to restore motor functions such as standing and stepping.
- Using rodent and swine SCI models, combined with spinal cord injury and spinal stimulation, to study electrophysiological and biomechanical biomarkers associated with spinal sensorimotor networks facilitated by emerging neuromodulation and neuroregeneration strategies to elucidate underlying mechanisms of action.

**Poster #47: Spinal Interneurons: essential elements of plasticity after cervical spinal cord injury**

Margo Randelman, Lyandysha Zholudeva, Michael Caplan, Tatiana Bezdudnaya, Michael Lane

*Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, PA, USA*

It is estimated that there are more than 180,000 new cases of spinal cord injury that occur world-wide each year. Around 17,700 of those occur within the United States of America. In addition, it is estimated that there are between 250,000 and 360,000 people living with spinal cord injury in the US alone. The majority of injuries (estimated at ~59% in 2017) occur at 'cervical' levels, or the level of the neck. Injuries at this level result in the most devastating outcomes, including impaired use of upper and lower extremities (arms and legs), impaired breathing, bladder and bowel function, and increased risk of chronic pain to name a few.

Plasticity, or more specifically in the present circumstance 'neuroplasticity', is a functional or anatomical change that can occur either spontaneously or be therapeutically driven, and will likely become permanent. For example, some limited spontaneous functional improvements can occur following spinal cord injury. This spontaneous recovery – or functional plasticity – may be due to coinciding anatomical changes.

Our research team is investigating the effects of cervical spinal cord injury and how recovery can be optimized. A primary focus of this work is on the functional consequences of cervical spinal cord injury (in particular how breathing function is impaired in awake and sleeping states - e.g. sleep disordered breathing) and what potential there is for progressive, spontaneous or therapeutically driven functional recovery – or functional 'plasticity'. A key focus of this research is on spinal interneurons - a unique population of cells that can adapt to the changing conditions of injury and form new networks capable of repair. They can also be harnessed therapeutically via activity-based therapies (e.g. rehabilitation) or modern cell therapy techniques. Advances in stem cell biology and cellular engineering have paved the way to a new era of cell transplantation. Harnessing the strengths of these methods, spinal interneurons can now be engineered for transplantation and spinal cord repair. Building upon this, activity-based training can be used to drive plasticity and connectivity within the injured spinal cord and transplanted cells.

Using pre-clinical models, the goal of our research team is to improve our understanding of plasticity after injury, and harness the strengths of these newly developed therapies to work toward improved outcomes following spinal cord injury.

**Poster #48: Title: Activating cell-intrinsic growth competency to promote axon regeneration after SCI**

Jian Zhong\*, Francesco Boato, Xiaofei Guan, Christina Torturo, Fabricio Nicola, Chase Freschlin.

*Burke Neurological Institute, Weill Cornell Medicine, New York.*

Contact: <http://burke.weill.cornell.edu/zhong-lab>

We have identified the B-RAF - MAP kinase signaling module as a strong driver of axon regeneration in animal models of traumatic CNS injury. The goal of our research now is to determine how activation of this pathway drives regeneration, and how it could translate into treatments for paralysis caused by spinal cord injury. Specifically, we pursue the following projects:

- 1. Uncover the molecular mechanisms of B-RAF-driven CST axon regeneration.** We hypothesize that activation of B-RAF enhances axonal transport, and in particular the translocation of ribosomes and growth-relevant mRNAs into the injured axon. We have thus begun a project to isolate and identify the mRNA species that are associated with ribosomes in the injured corticospinal tract (CST) of mice where B-RAF-driven regeneration is ongoing. This approach will yield a set of genes that are likely to be involved in CST axon regeneration and may well include “druggable” candidates.
- 2. Demonstrate *de novo* synaptogenesis and new connectivity of regenerating axons.** To support motor functional recovery, regenerating CST axons must form new synapses to re-establish connectivity with interneurons, lower motor neurons, and muscles. Direct evidence for the formation of new, active synapses has been lacking in animal models of SCI, even those that regain a measure of motor function. We are now testing a set of new genetically encoded anterograde transsynaptic tracers for their ability to label CST axons and their downstream target spinal interneurons. In collaboration with Chris Schaffer's and Chris Xu's groups at Cornell University, Ithaca, we apply 3-photon excitatory fluorescence (3PEF) microscopy to monitor neuronal activity in the spinal cord, in awake, moving mice. Transsynaptic tracing in mice expressing a genetically encoded calcium indicator will enable us to directly observe synaptic activity in spinal interneurons postsynaptically connected to the regenerating CST.
- 3. Regeneration of nociceptive and proprioceptive afferents after dorsal root crush injury.** Activation of B-RAF kinase in adult dorsal root ganglion neurons enables regeneration of ascending sensory axons across the dorsal root entry zone into the spinal grey matter after dorsal root crush injury (collaboration with Dr. Young-jin Son, Temple University). Recovery of sensory function will require the correct formation of new synapses between specific sensory axons and their target cells in the spinal cord. We therefore plan to characterize the distinct patterns and dynamics of regeneration and synaptogenesis displayed by the two major types of sensory afferents in this system, the proprioceptive and nociceptive axons.
- 4. High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) to promote CST axon regeneration.** Repetitive TMS is already used in the clinic to treat severe depression. In SCI model mice subjected to HF-rTMS, we have recently observed activation of RAF downstream effectors as well as significant CST axon regeneration. To begin to understand this phenomenon, we are collaborating with Dr. Aapo Nummenmaa's group (Harvard) to quantitatively model the TMS-induced electrical fields, in preparation for an initial feasibility and safety study of rTMS in SCI patients.