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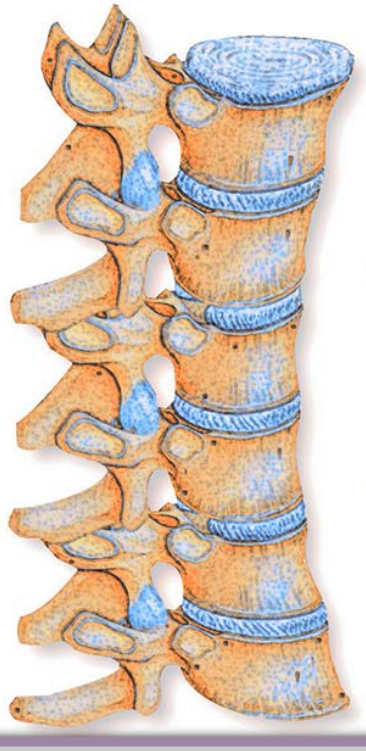

SPINAL CORD INJURY RESEARCH SYMPOSIUM

October 16 & 17, 2018

The Rockefeller University

Carson Family Auditorium

1230 York Avenue, New York, New York

NYS SCI Research Symposium 2018

The Rockefeller University

Carson Family Auditorium

PROGRAM COMMITTEE

Donald S. Faber, Ph.D., Albert Einstein College of Medicine, Florence and Irving Rubenstein University, Professor Emeritus

Bernice Grafstein, Ph.D., D.Sc.(hon.), Weill Medical College of Cornell University, Department of Physiology and Biophysics, Department of Brain and Mind Research Institute

Lorne Mendell, Ph.D., Stony Brook University, Department of Neurobiology and Behavior

Adam B. Stein, M.D., Chair and Professor, Donald and Barbara Zucker School of Medicine at Hofstra Northwell

ORGANIZING COMMITTEE

Andrea Garavelli, Director, Extramural Grants Administration, SCIRB

Jeannine Tusch, Health Program Administrator, Extramural Grants Administration, SCIRB

Special Thanks to our Sponsor:

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The Craig H. Neilsen Foundation is dedicated to research and programs to improve the quality of life for people living with spinal cord injury.

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GENERAL

INFORMATION

All sessions will take place in the Carson Family Auditorium.

MEALS

All meals and the reception on Tuesday evening will take place in the lobby outside of the Carson Family Auditorium.

POSTER SESSIONS

Poster Sessions 1 & 2 will take place in the lobby outside of the Carson Family Auditorium. Presenters can set up their poster as early as 8am on the day of their scheduled session. Please refer to the Poster Sessions section of the program book for poster assignments.

For more information about the NYS SCI Research Symposium and NYS SCIRB, visit **https://www.wadsworth.org/extramural/spinalcord**

NYS SCI RESEARCH SYMPOSIUM 2018

PROGRAM AT-A-GLANCE

Tuesday, October 16

8:00AM - 8:45AM	**Registration & Breakfast**
8:45AM - 9:00AM	**Welcoming Remarks**
9:00AM - 10:40AM	**Pharmacological Approaches to Spinal Cord Injury**
10:40AM -11:05AM	**Coffee Break**
11:05AM - 12:20PM	**Manipulating Spinal Function to Improve Functional Outcome After Spinal Cord Injury**
12:20PM - 1:05PM	**Lunch**
1:05PM - 2:45PM	**Spinal Stimulation for Recovery of Spinal Function After Spinal Cord Injury**
2:45PM - 3:10PM	**Coffee Break**
3:10PM - 4:50PM	**Strategies to Improve Repair of Damaged Pathways After Spinal Cord Injury**
5:30PM - 7:30PM	**Poster Session 1 & Reception**

Wednesday, October 17

8:00AM - 9:15AM	**Poster Session 2 & Breakfast**
9:15AM - 10:55AM	**Cellular Issues in Repairing the Damaged Spinal Cord**
10:55AM - 11:05AM	**Coffee Break**
11:05AM -1:00PM	**Translational Issues**
1:00PM -1:35PM	**Discussion & Closing Comments**
1:35PM - 2:00PM	**Lunch & Adjourn**

PROGRAM SCHEDULE
TUESDAY, OCTOBER 16, 2018

8:00AM-8:45AM Registration & Breakfast

8:45AM-9:00AM (A) Welcoming Remarks
Lorne Mendell, Ph.D., Stony Brook University

9:00AM-10:40AM (B) Pharmacological Approaches to Spinal Cord Injury
Chair: Fraser J. Sim, Ph.D., University at Buffalo

- (B1) 9:00AM-9:50AM
  Restoring Intrinsic Regenerative Ability to Axons
  James Fawcett, Ph.D., University of Cambridge
- (B2) 9:50AM-10:15AM
  Promoting Recovery from Acute SCI by Drug Repurposing
  Mark David Noble, Ph.D., University of Rochester Medical Center
- (B3) 10:15AM-10:40AM
  Creating a Pro-Regenerative Environment in the Spinal Cord After Injury using Biodegradable Microbeads
  Sally Temple, Ph.D., Neural Stem Cell Institute

10:40AM-11:05AM Coffee Break

11:05AM-12:20PM (C) Manipulating Spinal Function to Improve Functional Outcome After Spinal Cord Injury
Chair: Bernice Grafstein, Ph.D., D.Sc.(hon.), Weill Medical College of Cornell University

- (C1) 11:05AM-11:55AM
  Neural Devices to Promote Plasticity and Recovery Following Spinal Cord Injury
  Chet T. Moritz, Ph.D., University of Washington
- (C2) 11:55AM-12:20PM
  The Spinal Cord: A Negotiated Equilibrium
  Jonathan R. Wolpaw, M.D., National Center for Adaptive Neurotechnologies, Wadsworth Center, NYS Department of Health

12:20PM-1:05PM Lunch

1:05PM-2:45PM (D) Spinal Stimulation for Recovery of Spinal Function After Spinal Cord Injury
Chair: Thomas N. Bryce, M.D., Icahn School of Medicine at Mount Sinai

- (D1) 1:05PM-1:55PM
  A Continuum of Strategies for Neuromodulation After Spinal Cord Injury
  Susan J. Harkema, Ph.D., University of Louisville

- (D2) 1:55PM-2:20PM
  Transspinal Stimulation: A Neuroprosthesis for Brain and Spinal Cord Neuromodulation Driving Recovery of Arm and Leg Movement
  Maria Knikou, P.T., Ph.D., The City University of New York
- (D3) 2:20PM-2:45PM
  Electro-Magnetic Stimulation (EMS), NMDA Receptors, Neuromodulation: From Animal Study to Humans and Back to Animals
  Victor L. Arvanian, Ph.D., DSi., Northport VA Medical Center and Stony Brook University

2:45PM-3:10PM Coffee Break

3:10PM-4:50PM (E) Strategies to Improve Repair of Damaged Pathways After Spinal Cord Injury
Chair: Donald S. Faber, Ph.D., Albert Einstein College of Medicine

- (E1) 3:10PM-4:00PM
  Overcoming Axonal Growth Limitation After Spinal Cord Injury: Discovery of Intrinsic Molecular Mechanisms and Translational Development of Extrinsic Inhibitor Blockade
  Stephen M. Strittmatter, M.D., Ph.D., Yale School of Medicine
- (E2) 4:00PM-4:25PM
  Modulating Neural Activity to Repair the Corticospinal System After Spinal Cord Injury
  John H. Martin, Ph.D., City University of New York School of Medicine at CCNY
- (E3) 4:25PM-4:50PM
  Learning to Move After Spinal Cord Injury
  Jason B. Carmel, M.D., Ph.D., Columbia University College of Physicians and Surgeons

5:30PM-7:30PM Poster Session 1 & Reception

PROGRAM SCHEDULE
WEDNESDAY, OCTOBER 17, 2018

8:00AM-9:15AM Poster Session 2 & Breakfast

9:15AM-10:55AM (F) Cellular Issues in Repairing the Damaged Spinal Cord
Chair: Kristjan T. Ragnarsson, M.D., Icahn School of Medicine at Mount Sinai

- (F1) 9:15AM-10:05AM
  Long Term White Matter Changes After Spinal Cord Injury
  Dana McTigue, Ph.D., Ohio State University
- (F2) 10:05AM-10:30AM
  In Vivo Imaging of Cellular Dynamics and Neural Activity in the Spinal Cord of Mice
  Chris B. Schaffer, Ph.D., Cornell University
- (F3) 10:30AM-10:55AM
  Systemic Immune Changes After Spinal Cord Injury
  Ona E. Bloom, Ph.D., The Feinstein Institute for Medical Research

10:55AM-11:05AM Coffee Break

11:05AM-1:00PM (G) Translational Issues
Chair: Adam B. Stein, M.D., Donald and Barbara Zucker School of Medicine at Hofstra Northwell

- (G1) 11:05AM-11:55AM
  Bench to Bedside and Back: Translational Research in Acute Spinal Cord Injury
  Brian Kwon, M.D., Ph.D., University of British Columbia
- (G2) 11:55AM-12:25PM
  Neural Bypass Technology for Restoring Functional Hand Movement in Tetraplegia
  Chad Bouton, M.S., The Feinstein Institute for Medical Research
- (G3) 12:25PM-12:50PM
  Robotics to Restore and Retrain Human Movements
  Sunil Agrawal, Ph.D., Columbia University
- (G4) 12:50PM-1:00PM
  Functional Outcome Changes After Exoskeletal-Assisted Walking during Acute SCI Inpatient Rehabilitation: A Pilot Study
  Chung-Ying Tsai, Ph.D., Icahn School of Medicine at Mount Sinai

1:00PM-1:35PM Discussion and Closing Comments
Chairs: Adam B. Stein, M.D. and Lorne Mendell, Ph.D.

1:35PM-2:00PM Lunch & Adjourn

WELCOME

(A) WELCOMING REMARKS
8:45AM-9:00AM

Lorne Mendell, Ph.D.
SUNY Distinguished Professor
Department of Neurobiology and Behavior
Stony Brook University

On behalf of the NYS Spinal Cord Injury Research Board and the NYS Department of Health, I would like to welcome you and thank you for your interest and participation in the NYS SCI Research Symposium.

The Symposium provides an opportunity for NYS researchers to present their research and discoveries in spinal cord injury (SCI) mechanisms. Attendees will hear from invited international and national researchers on a variety of SCI research topics. This will add significantly to the experience for many of our NYS scientists, clinicians and students interested and involved in SCI research.

Our program book includes abstracts from invited speakers and is organized to reflect the two-day agenda. For more information related to the Board and Program, please visit our website here: https://www.wadsworth.org/extramural/spinalcord. If you need assistance, please stop by the registration desk conveniently located directly outside of the Carson Family Auditorium.

NYS SCIRB Members

Lorne Mendell, Ph.D., Chair
Stony Brook University, SUNY

Donald S. Faber, Ph.D., Vice Chair
Albert Einstein College of Medicine at Yeshiva University

Thomas N. Bryce, M.D.
Icahn School of Medicine at Mount Sinai
The Mount Sinai Medical Center

Anthony Oliver Caggiano, M.D., Ph.D.
Acorda Therapeutics, Inc.

Michael E. Goldberg, M.D.
Columbia University College of Physicians and Surgeons

Bernice Grafstein, Ph.D., D.Sc.(hon.)
Weill Medical College of Cornell University

Keith Gurgui
Resource Center for Accessible Living

Nancy A. Lieberman
Skadden, Arps, Slate, Meagher & Flom, LLP

Gary D. Paige, M.D., Ph.D.
Professor Emeritus of Neurology
Chair Emeritus of Neurobiology and Anatomy
University of Rochester, School of Medicine & Dentistry

Kristjan T. Ragnarsson, M.D.
Icahn School of Medicine at Mount Sinai

Fraser J. Sim, Ph.D.
Associate Professor
Neuroscience, Pharmacology and Toxicology, GGB
University at Buffalo, Jacobs School of Medicine and Biomedical Sciences

Adam B. Stein, M.D.
Chair and Professor, Donald and Barbara Zucker School of Medicine at Hofstra Northwell

SPEAKER ABSTRACTS

(B) PHARMACOLOGICAL APPROACHES TO SPINAL CORD INJURY
9:00AM-10:40AM
Chair: Fraser J. Sim, Ph.D., University at Buffalo

(B1) RESTORING INTRINSIC REGENERATIVE ABILITY TO AXONS
9:00AM-9:50AM

James Fawcett, Ph.D.[1]
Professor and Chairman
John van Geest Centre for Brain Repair
University of Cambridge, UK

CNS axons fail to regenerate because of the inhibitory environment and because of an intrinsic lack of regenerative ability. Why does this happen and how can regeneration be stimulated? We have studied these problems through the focus of integrin-mediated axon growth and axonal transport. Integrins can be a therapeutic and can enhance regeneration, and they are also a tool with which one can study the biology of growing and non-regenerating axons to indicate what has gone wrong with growth mechanisms in mature CNS axons. In order to grow through the extracellular matrix axons must first express appropriate integrins. The main matrix glycoprotein in the damaged CNS is tenascin-C, but tenascin-C binding integrins are absent in the mature CNS. For migratory events on tenascin-C alpha9 beta1 is the most effective integrin. In cultures alpha9 transfection gives sensory axons the ability to grow prolifically on tenascin, but transduction of DRG neurons in vivo only gives modest regeneration. The problem is that the CNS inhibitory molecules CSPG and NogoA inactivate integrins, and for integrin manipulation to be effective it has to be combined with an integrin activator, kindlin1. Co-expresson of alpha9 integrin and kindlin1 in sensory neurons enables profuse long-distance axon growth in the spinal cord and sensory recovery.

Neurons in the CNS lose regenerative ability with maturity. Studying integrins as an example of a growth-related molecule can reveal reasons for this loss. Transport of integrins in corticospinal axons becomes blocked at the axon initial segment as axons mature and integrins are only seen on dendrites. Many other growth-related molecules are also excluded from mature axons, including ribosomes, neurotrophin receptors and other growth factor receptors. The lack of these receptors in axons leads to low PI3K activation and low PIP3 generation. How does this transport block occur? Integrin transport and trafficking in axons relies on the GTPases Rab11 and Arf6 whose activation state regulates transport and trafficking. Two Arf6 GEFs including EFA6 which is concentrated in the axon initial segment are upregulated during maturation to reverse integrin transport to retrograde, so preventing integrin entry into axons. Interventions to change Arf6 activation, enhance PIP3 signalling and demolish the axon initial segment all promote regeneration.

A reason for the low intrinsic ability of axons to regenerate in the CNS is because mature axons become increasingly specialized, with exclusion of many molecules needed for activation of signalling pathways and axon growth. They therefore lack the ability to interact with their environment, and to generate signals to drive regeneration.

[1]James Fawcett qualified in Medicine in Oxford and London. After a period in clinical practice he studied for a Ph.D. under Michael Gaze at National Institute for Medical Research in Mill Hill. Five years at the Salk Institute followed, after which he moved to Cambridge University, first in Physiology then as Chairman of the Brain Repair Centre. His main interest is the restoration of CNS function lost through spinal cord injury, neurodegenerative disease and ageing. He has focused on activation of axon regeneration and plasticity

through manipulation of the extracellular matrix and integrins. He also works on interfacing electronics with the damaged nervous system and on the design of protocols for clinical trials in spinal cord injury.

(B2) PROMOTING RECOVERY FROM ACUTE SCI BY DRUG REPURPOSING
9:50AM-10:15AM

Mark David Noble, Ph.D.
University of Rochester Medical Center

The urgent need to find new treatments for a variety of neurological injuries and diseases would be most effectively addressed by focusing attention on discovery of new uses of agents already approved for other clinical applications. We have been approaching this effort in multiple ways, with particularly promising results emerging from the study of a drug once thought to be of interest (and since abandoned) in the treatment of some cases of chronic SCI. We will present data demonstrating promising effects on multiple components of SCI, including promotion of durable recovery, by a two-week treatment with our current lead drug. Critically, we are able to obtain striking benefits even when we start treatment 24 hours after injury, thus providing an important extension of the opportunity for intervention in acute injury. We also will present data on other injury paradigms and benefits relevant to promoting recovery after traumatic SCI. Finally, we also will consider several of the challenges and variables that require attention when moving a promising discovery forward in a pre-clinically relevant manner.

(B3) CREATING A PRO-REGENERATIVE ENVIRONMENT IN THE SPINAL CORD AFTER INJURY USING BIODEGRADABLE MICROBEADS
10:15AM-10:40AM

Sally Temple, Ph.D.
Neural Stem Cell Institute
Rensselaer, NY

Elizabeth Fister, Ph.D., Natasha Lowry, M.D., Ph.D., Thomas Kiehl, Ph.D.
Neural Stem Cell Institute
Rensselaer, NY
Aileen Anderson, Ph.D., Hal Nguyen, Ph.D.
University of California, Irvine, CA

Spinal cord injury (SCI) affects more than a million individuals in the US. Most were injured at a young age and suffer life-long consequences of paralysis and numerous medical complications. Current treatments are symptomatic, and do not result in recovery. Research into novel treatments that will improve regeneration and repair after SCI are imperative, as there is great unmet medical need.

Shortly after SCI, there is an influx of inflammatory cells, which contributes to secondary damage. Neutrophils arrive within hours of the injury, releasing cytokines and creating reactive oxygen species that cause further damage. Macrophage populations arrive in two waves, documented in murine models, - the first of pro-inflammatory M1 cells at 3-7 days after the injury and the second of pro-regenerative M2 cells about 40 days later. Controlling this immune response is important to reduce spinal cell loss, preserve functionality and improve regenerative responses. Immunomodulatory intervention to dampen negative effects must be timed appropriately for optimal benefit.

To define the types and state of immune cells after SCI in more detail, we have isolated these cells by fluorescent activated cell sorting (FACS) at different times after contusion injury to enable us to assess the

gene expression of individual cells in a comprehensive manner. We have identified different populations of immune cells present in the acute and chronically injured spinal cord. Further, we have developed bioengineered microbeads made of a biodegradable, biocompatible and FDA approved material to deliver sustained IL10 to the infiltrating macrophages to switch these toward the beneficial M2 type. These IL10 beads can be delivered to the injury site with the goal of counteracting inflammatory processes and promoting a pro-regenerative environment. Our preliminary findings indicate a beneficial effect of delivering IL10 after acute contusion injury in rats.

Previously we demonstrated that supplying sustained release sonic hedgehog growth factor (SHH) to the injured spinal cord in mice acutely after the injury improved behavioral recovery. Histological analysis revealed that sustained SHH treatment reduced astrocytic scarring, increased axonal sprouting and sparing, and improved behavioral recovery. In preliminary studies we have found that sustained SHH treatment through microbead implantation is beneficial in chronically injured rats with a contusion injury. In the future, we will assess the combination of IL10 and SHH sustained release bead administration on recovery from SCI.

This project, funded through a NYS SCIRP CART award, adds to our overall understanding of the complex immune response after SCI and will determine whether altering the local injured environment by administering IL10 and SHH sustained release bioengineered microbeads at specific times after injury can reduce the inflammatory environment and promote repair after SCI. Our goal is to translate positive findings made in animal models to develop safe and effective SCI regenerative therapies for patients.

(C) MANIPULATING SPINAL FUNCTION TO IMPROVE FUNCTIONAL OUTCOME AFTER SPINAL CORD INJURY

11:05AM-12:20PM

Chair: Bernice Grafstein, Ph.D., D.Sc.(hon.), Weill Medical College of Cornell University

(C1) NEURAL DEVICES TO PROMOTE PLASTICITY AND RECOVERY FOLLOWING SPINAL CORD INJURY

11:05AM-11:55AM

Chet T. Moritz, Ph.D.[2]
Allen Distinguished Investigator
Associate Professor
Division of Physical Therapy
Departments of Rehabilitation Medicine and Physiology & Biophysics
Co-Director, Center for Sensorimotor Neural Engineering
University of Washington Institute for Neuroengineering (UWIN)
Program in Neuroscience
University of Washington

Neuroprosthetic devices have tremendous potential to improve quality of life after brain and spinal cord injury. Neuroprostheses that record and stimulate neural activity have progressed from animal studies to human trials, including the approach of using brain activity to control Functional Electrical Stimulation (FES) of paralyzed hand muscles. Another promising method for restoring movement and enhancing rehabilitation is direct stimulation of the spinal cord. Both transcutaneous and intraspinal stimulation can activate neural circuits distal to an injury, leading to either direct muscle contraction or facilitating therapy and enabling volitional movements. Optical stimulation of the spinal cord and visceral organs is another promising approach to achieve specific neural activation by leveraging optogenetic techniques. Our goal is to leverage emerging neural engineering techniques to develop technologies that improve function and quality of life following spinal cord injury.

[2]Chet T. Moritz received his Ph.D. from the University of California, Berkeley, followed by post-doctoral training at the University of Colorado. A second post-doc at the University of Washington began his interest in brain-

computer interfaces and neural devices to treat paralysis. He is now an Associate Professor in the departments of Rehabilitation Medicine, Electrical Engineering, and Physiology & Biophysics. He was named an Allen Distinguished Investigator and appointed to the Christopher & Dana Reeve International Consortium on Spinal Cord Repair. Chet serves as the Co-Director for the Center for Sensorimotor Neural Engineering, and NSF Engineering Research Center (ERC). He is also the founding director of the Washington Spinal Cord Injury Consortium (WASCIC). Chet directs the Restorative Technologies Laboratory (RTL) which focuses on developing technologies to treat paralysis due to spinal cord injury.

(C2) THE SPINAL CORD: A NEGOTIATED EQUILIBRIUM
11:55AM-12:20PM

Jonathan R. Wolpaw, M.D.
National Center for Adaptive Neurotechnologies
Wadsworth Center, NYS Department of Health

The belief that the spinal cord is hardwired is no longer tenable. Like the rest of the CNS, the spinal cord changes during growth and aging, when new motor behaviors are acquired, and in response to trauma and disease. This presentation describes a new model of spinal cord function that reconciles its recently appreciated plasticity with its long recognized reliability as the final common pathway for behavior.

According to this model, the substrate of each motor behavior comprises brain and spinal plasticity: the plasticity in the brain induces and maintains the plasticity in the spinal cord. Each time a behavior occurs, the spinal cord provides the brain with performance information that guides changes in the substrate of the behavior. All the behaviors in the repertoire undergo this process concurrently; each repeatedly induces plasticity to preserve its key features despite the plasticity induced by other behaviors. The aggregate process is a negotiation among the behaviors: they negotiate the properties of the spinal neurons and synapses that they all use. The ongoing negotiation maintains the spinal cord in an equilibrium – a negotiated equilibrium – that serves all the behaviors. This new model of spinal cord function is supported by laboratory and clinical data, makes predictions borne out by experiment, and underlies a new approach to restoring function to people with spinal cord injury or other neuromuscular disorders. Further studies are needed to test its generality, to determine whether it may apply to other CNS areas such as the cerebral cortex, and to develop its therapeutic implications.

(D) SPINAL STIMULATION FOR RECOVERY OF SPINAL FUNCTION AFTER SPINAL CORD INJURY
1:05PM-2:45PM
Chair: Thomas N. Bryce, M.D., Icahn School of Medicine at Mount Sinai

(D1) A CONTINUUM OF STRATEGIES FOR NEUROMODULATION AFTER SPINAL CORD INJURY
1:05PM-1:55PM

Susan J. Harkema, Ph.D.[3]
Professor
Department of Neurological Surgery, University of Louisville
Louisville, KY

We have previously shown that chronic, motor complete SCI individuals can progressively recover voluntary and standing ability when lumbosacral spinal cord epidural stimulation (scES) is applied with task- and individual-specific parameters. The aim of this study was to investigate the effects of two different activity-based training paradigms with scES on standing ability, and to determine whether standing and stepping can be concurrently trained without limiting the recovery of standing in individuals with chronic complete SCI using

scES. Seven individuals with chronic, motor complete SCI were implanted with a spinal cord epidural stimulation unit. All research participants received an implant of a 16-electrode array on the dura (L1-S1 cord segments, T11-L1 vertebrae). Four individuals performed approximately 80 sessions of stand training with scES (5 days/week; 1 hour per session) followed by 80 sessions of step training with scES (Group 1). Three other individuals (Group 2) performed an interleaving stand-step training with scES, which consisted of stand training and step training that alternated every session until the same amount of training as in the previous protocol (~ 160 sessions) was achieved. The interleaving stand-step training with scES promoted significant recovery of standing ability in three chronic complete SCI individuals, and seemed more effective than the previous paradigm in which stand training was completed prior to step training. This indicates that the human spinal circuitry can learn to generate motor patterns effective for standing while also stepping, as long as both standing and stepping are practiced. We also discovered that the human lumbosacral circuitry was transformed into functional states that generated independent steps when optimized epidural stimulation was present, task specific proprioception for stepping was ongoing; but this only occurred when the individual was driving specific intent for walking. This unexpected finding showed that de novo functional supraspinal connections had emerged to reestablish control of aspects of locomotion in individuals who had been clinically diagnosed with motor complete spinal cord injury. The spinal circuitry has potential to drive recovery after severe spinal cord injuries if provided with the appropriate retraining in a specific central state of excitability.

Chronic low blood pressure and orthostatic hypotension remain challenging clinical issues after severe SCI, affecting health, rehabilitation, and quality of life. In four participants with chronic hypotension and orthostatic hypotension, individual-specific CV-scES configurations (anode and cathode electrode selection, voltage, frequency, and pulse width) were identified to maintain systolic blood pressure within targeted normative ranges without skeletal muscle activity of the lower extremities as assessed by electromyography. These individuals completed five 2-hour sessions using CV-scES in an upright, seated position during measurement of blood pressure and heart rate. For each research participant there were statistically significant increases in mean arterial pressure in response to CV-scES that was maintained within normative ranges and reproducible over the five sessions with concomitant decreases or no changes in heart rate. Orthostatic hypotension resolved with CV-scES and after Daily CV-scES Training. A similar response was observed post Daily CV-scES Training when presented with orthostatic stress even without stimulation after 80 daily training sessions. Improved resting systolic blood pressure and orthostatic tolerance indicates CV-scES had effects associated with adaptive plasticity that stabilized cardiovascular and autonomic regulatory systems after chronic cervical spinal cord injury. Epidural stimulation applied to motor-complete SCI demonstrates significant potential for not only motor recovery, but autonomic recovery as well: physiological and motor behavior can respond to stimulation of the lumbosacral cord when targeted to a physiological response or motor tasks.

[3]Susan J. Harkema, Ph.D., holds the Owsley B. Frazier Rehabilitation Chair in Neurological Surgery and is the Associate Director of the Kentucky Spinal Cord Injury Research Center at the University of Louisville. Over the last 20 years, her research has focused on neural plasticity of spinal networks and recovery of function after spinal cord injury. Her more recent studies have shown that people with chronic paralysis can regain the ability to voluntarily move their legs and stand independently with epidural stimulation. This broadened the scope of the translational research program to include technology development to improve implantable epidural stimulators. Dr. Harkema has maintained an NIH funded research program since 1998 in neuroplasticity after human spinal cord injury and served as the Director of an NIH-funded program project grant from 1998-2008.

Dr. Harkema has published more than 180 scholarly manuscripts and book chapters. She has delivered over 100 worldwide lectures and keynotes, has been a grant reviewer for the NIH, Roman Reed, Mission Connect, FISM Society, and has sat on numerous advisory boards and review panels. Many of her 28 mentored graduate students and post-doctoral fellows have excelled in their careers.
Dr. Harkema has co-authored seven United States patents and has received several honors and awards throughout her career. In 2007, the National Spinal Cord Injury Association nominated her into the SCI Hall of Fame for Achievement in Research in Quality of Life, and in 2008, Dr. Harkema was a co-recipient of the Reeve-

Irvine Research Medal, awarded to individuals who have made critical contributions to promoting repair of the damaged spinal cord and recovery of function. In 2011, Dr. Harkema received the Difference Maker Award from the Rick Hansen Foundation and the Breakthrough Award from Popular Mechanics. She received the John Stanley Coulter Award for significant contribution to the field of rehabilitation by the ACRM in 2012 and received the Innovator of the Year award from Business First in 2014.

Dr. Harkema earned her Bachelor of Science and Ph.D. from Michigan State University and conducted her postdoctoral fellowship in neurophysiology at the University of California, Los Angeles.

(D2) TRANSSPINAL STIMULATION: A NEUROPROSTHESIS FOR BRAIN AND SPINAL CORD NEUROMODULATION DRIVING RECOVERY OF ARM AND LEG MOVEMENT
1:55PM-2:20PM

Maria Knikou, P.T., Ph.D.
The City University of New York, College of Staten Island

Spinal cord injury (SCI) results in significant movement impairments. Several therapeutic interventions are utilized with the aim to diminish or decrease the detrimental complications of SCI. Non-invasive interventions that can strengthen weak neuronal synapses connecting the spinal cord with the brain or fully optimize spinal neural circuits are in great need. In this talk, I will present evidence supporting transspinal stimulation as a novel neuroprosthesis to augment existing function or bypass deficits caused by injury to the spine. In healthy humans, transspinal stimulation over the cervicothoracic and thoracolumbar enlargement produces transspinal evoked potentials (TEPs) in proximal and distal arm and leg muscles that have latencies similar to monosynaptic reflexes. Transspinal stimulation is known to increase corticospinal excitability and produce inhibition and/or facilitation of the soleus H-reflex based on the timing between afferent inputs and transspinal stimuli. Further, when transspinal stimulation is paired with transcortical stimulation, neuromodulation occurs concomitant at multiple levels of the nervous system. In people with SCI, transspinal stimulation over the cervicothoracic region improves voluntary arm muscle strength that is mediated through strengthening of corticospinal neural connections. Transspinal and transcortical paired stimulation delivered during the mid-stance phase of robotic gait training in persons with motor incomplete and complete SCI, promotes a physiological phase-dependent modulation pattern of the soleus H-reflex during robotic assisted walking. Our ongoing clinical trials strongly supports the notion that transspinal stimulation can be utilized to produce targeted brain and spinal cord neuromodulation protocols driving recovery of arm and leg movement after SCI in humans.

(D3) ELECTRO-MAGNETIC STIMULATION (EMS), NMDA RECEPTORS, NEUROMODULATION: FROM ANIMAL STUDY TO HUMANS AND BACK TO ANIMALS
2:20PM-2:45PM

Victor L. Arvanian, Ph.D., DSi.
Northport VA Medical Center and Stony Brook University

Petrosyan HA, Sisto SA, Liang L, Zou C, Leone C, Tesfa A, Fahmy M.

Our recent intracellular recordings revealed attenuated excitability of the surviving axons and diminished synaptic function at individual motoneurons, even incomplete SCI in adult rats. Synapses are known to function in activity-dependent manner in human and rat spinal cord. In attempt to electrically activate deep neural structures using non-invasive approach, we used EMS at spinal levels. We found that repetitive administration of spinal EMS

partially restored excitability of the surviving axons and improved transmission to motoneurons and then to leg muscles in chronically SCI rats. These effects of spinal EMS required function of NMDA receptors at motoneurons synapses. Using parameters of SEMS found to induce strengthening transmission in rats, we currently examine effects of spinal EMS applied alone or in combination with EMS of leg muscles in healthy and SCI humans. Literature reports indicate that SCI affects threshold intensity and frequency dependent depression (FDD) of H-reflex in humans. We measured soleus M-wave and H- reflex recruitment curves using peripheral tibial nerve stimulation before EMS, after spinal EMS and after leg EMS, respectively. To study FDD of H-reflex stim current was set to evoke 40% of H-max, using 0.2, 1, 2 and 5 Hz stim rate. Baseline measurements (prior EMS) revealed a less steep (flatter) rise phase and more prolonged plateau of the recruitment curve of H-reflex, as well as a lesser depression rate of FDD in SCI vs healthy participants. In both healthy and SCI subjects, 1st application of spinal EMS for 25mins induced substantial facilitation of both M-response and H-reflex; this associated with a significant leftward shift of the recruitment curves for M- and H-responses and a marked decrease in the threshold currents to evoke H- and M-responses. 2nd follow-up application of spinal EMS did not induce further changes, thus indicating that effects of spinal EMS reached its maximum after initial 1st 25 min of EMS. However, EMS application over leg muscles induced further facilitation of M-wave and H-response. Results of this on-going study suggest that EMS over spinal level and leg muscles exert their effects on H-reflex through different mechanisms. Although effects of spinal/leg EMS on threshold intensity of H-reflex were consistent and statistically significant among participants, modulation of FDD of the H-reflex was less consistent and was not observed in all participants. To understand cellular mechanisms underlying effects of EMS in humans, we examine effects of spinal EMS on properties of H-reflex in rats, under condition of acute intraspinal injections of specific antagonists of glutamate and GABA receptors. Importantly, one SCI participant who was engaged in 20 min exercise training sessions (NUSTEP exercise machine) after completion of spinal/leg EMS, reported an increase in sensation and function for the first time after 12 years post-SCI. It is important to note that this subject had been performing similar exercise on a regular basis prior to this study without functional changes. Results suggest that spinal/leg EMS stimulation combined with exercise may be a potential approach in clinics for a variety of spinal or peripheral nerve conditions.

(E) STRATEGIES TO IMPROVE REPAIR OF DAMAGED PATHWAYS AFTER SPINAL CORD INJURY
3:10PM-4:50PM
Chair: Donald S. Faber, Ph.D., Albert Einstein College of Medicine

(E1) OVERCOMING AXONAL GROWTH LIMITATION AFTER SPINAL CORD INJURY: DISCOVERY OF INTRINSIC MOLECULAR MECHANISMS AND TRANSLATIONAL DEVELOPMENT OF EXTRINSIC INHIBITOR BLOCKADE
3:10PM-4:00PM

Stephen M. Strittmatter, M.D., Ph.D.[4]
Vincent Coates Professor of Neurology
Professor of Neuroscience
Director, Cellular Neuroscience, Neurodegeneration and Repair Program
Director, Memory Disorders Clinic
Director, Alzheimer Disease Research Center
Yale University School of Medicine

After adult mammalian traumatic Spinal Cord Injury (SCI), axonal growth is severely restricted by the extracellular environment surrounding the axon and by the intrinsic growth state of the neuron.

Amongst extrinsic inhibitors, proteins derived from oligodendrocytes and myelin contribute to inhibition and include Nogo, MAG and OMgo. These ligands interact with the NgR1 neuronal receptor with high affinity. The inhibitor effects can be negated by a soluble NgR1-Fc decoy receptor. The preclinical evidence

supporting NgR1-Fc treatment benefit in rodent and non-human primate SCI models even long after injury will be discussed. The path to clinical development of NgR1-Fc treatment for chronic cervical incomplete SCI will be delineated.

Certain neuronal proteins also limit axonal growth independently of the extracellular environment in a cell autonomous manner. We used a genome-wide loss-of-function screen for factors limiting axonal regeneration from cerebral cortical neurons in vitro. Knockdown of 16,007 individual genes identified 580 significant phenotypes. These molecules share no significant overlap with those suggested by previous expression profiles. There is enrichment for genes in pathways related to transport, receptor binding, and cytokine signaling, including Socs4 and Ship2. Among transport regulating proteins, Rab GTPases are prominent. In vivo assessment with C. elegans validates a cell-autonomous restriction of regeneration by Rab27. Mice lacking Rab27b show enhanced retinal ganglion cell axon regeneration after optic nerve crush and greater motor function and raphespinal sprouting after spinal cord trauma. Silencing of multiple additional hits from the screen in retinal ganglion cells results an in vivo optic nerve regeneration phenotype. Thus, a comprehensive functional screen reveals multiple pathways restricting axonal regeneration and neurological recovery after injury.

[4]Stephen M. Strittmatter earned his undergraduate degree from Harvard College, summa cum laude, in 1980. He completed M.D. and Ph.D. training at Johns Hopkins in 1986 with mentorship from Solomon H. Snyder, M.D. He then moved to Massachusetts General Hospital for a medical internship and an Adult Neurology residency. While at Massachusetts General Hospital, he worked as a Research Fellow with Mark Fishman, M.D., exploring the molecular basis of axonal guidance. After a year as Fellow, Dr. Strittmatter served briefly as an Assistant Professor at Harvard Medical School before moving to Yale University in 1993.

He currently holds the Vincent Coates Professorship of Neurology and co-founded the Yale Program in Cellular Neuroscience, Neurodegeneration and Repair. His research on axonal growth during development and regeneration has been recognized by honors from the Ameritec Foundation, the John Merck Fund, the Donaghue Foundation, the McKnight Foundation, the Jacob Javits Award of the NINDS and the American Academy of Neurology.

(E2) MODULATING NEURAL ACTIVITY TO REPAIR THE CORTICOSPINAL SYSTEM AFTER SPINAL CORD INJURY

4:00PM-4:25PM

John H. Martin, Ph.D.
Department of Molecular, Cellular, and Biomedical Science
City University of New York School of Medicine at CCNY, NY
Neuroscience Program City University of New York Graduate Center, NY

Preston T.J.A Williams, Yu-Qiu Jiang, Neela Zareen, Muneshia Shinozaki
Department of Molecular, Cellular, and Biomedical Science
City University of New York School of Medicine at CCNY, NY

Alzahra Amer
Neuroscience Program City University of New York Graduate Center, NY

Most spinal cord injuries are incomplete. An important target for neural repair to restore lost motor function is to promote the connections of spared descending spinal pathways with spinal motor circuits. Whereas there are many different descending pathways, the corticospinal tract (CST) is most associated with skilled motor functions. CST loss following injury leads to movement impairments and paralysis. To restore motor function after spinal cord injury will require repair of the damaged CST.

Our development studies identified that neural activity of the corticospinal motor system is critical for establishing specific and strong connections between the CST and spinal motor circuits for arm control. These developmental studies have informed neural activity-based strategies for repair of the damaged CST in maturity. Neuromodulatory approaches can be used to increase the activity of the motor cortex, the principal origin of the CST, and the spinal cord.

An important objective of our studies is to identify the effects of motor cortex and spinal cord neuromodulation on the function and anatomical connections of the corticospinal motor system in healthy animals and after cervical contusion injury. We use phasic motor cortex electrical and optical stimulation to activate motor cortex neurons and trans-spinal direct current stimulation (tsDCS) to modulate the excitability of spinal cord neurons.

In my presentation I will discuss how lesion of the CST, selectively or after cervical SCI, not only produces motor impairments, but also a complex set of maladaptive trans-neuronal structural changes in spinal circuits. Importantly, these changes can be replicated by the loss of motor cortex activity, which does not lesion the CST projection. I will show that increasing CST activity in maturity by motor cortex stimulation activates a growth program that promotes CST axon sprouting and the formation of spinal synaptic connections. tsDCS augments spinal cord activity and, together with motor cortex stimulation, rescues caudal spinal circuits from maladaptive trans-neuronal changes after injury. In turn, implementing these neuromodulatory approaches promotes recovery of skilled motor function after a cervical spinal injury.

In conclusion, our results show that neuromodulatory approaches, which can be implemented non-invasively or minimally-invasively, can produce long-lasting adaptive structural changes to the corticospinal system and parallel improvement in motor skills after injury. Knowledge of the effects of modulating corticospinal system activity informs the mechanisms underlying anatomical and functional changes after injury and contributes to development of therapies to help restore function.

Supported by NIH (JHM: 4R01NS064004) Craig H. Neilsen Foundation (NZ: 385743); NYS SCIRB (JHM: C30606GG, C31291GG; AA: C30860GG)

(E3) LEARNING TO MOVE AFTER SPINAL CORD INJURY
4:25PM-4:50PM

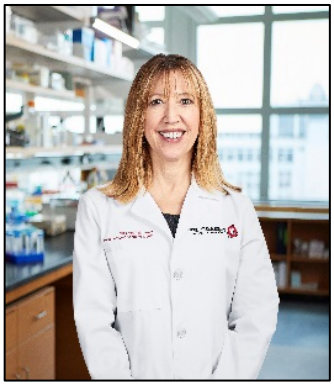
Jason B. Carmel, M.D., Ph.D.
Columbia University College of Physicians and Surgeons

Motor learning changes nervous system structure and function. We have sought to harness learning processes to restore function after spinal cord injury. I will discuss three New York SCIRP funded studies that adopt this approach to neural repair. First, we have paired brain and spinal cord stimulation to converge at the level of the spinal cord. Paired stimulation strengthens motor responses to electrical stimulation and improves forelimb function in rats with cervical contusion injury. Paired stimulation drives both short-term physiological and long-term anatomical changes. Second, we combined electrical stimulation and behavioral training in two ways, either simultaneously or by delaying the training until two weeks after stimulation. Combining stimulation and training caused large improvements in function, and this did not differ between the two paradigms. Electrical stimulation caused large-scale outgrowth of spinal axons, while training strongly improved function. Finally, we have tested the effects of 4-aminopyridine (4-AP), which raises excitability by blocking potassium channels, on motor learning. 4-AP increases excitability of intact motor circuits, but the effects on damaged circuits was even larger. 4-AP is also hypothesized to improve motor learning, which is currently being tested. Thus, divergent interventions that use learning mechanisms—convergent stimuli, training, and pharmacology—can improve function after spinal cord injury.

SPEAKER ABSTRACTS

(F) CELLULAR ISSUES IN REPAIRING THE DAMAGED SPINAL CORD
9:15AM-10:55AM
Chair: Kristjan T. Ragnarsson, M.D., **Icahn School of Medicine at Mount Sinai**

(F1) LONG TERM WHITE MATTER CHANGES AFTER SPINAL CORD INJURY
9:15AM-10:05AM



Dana McTigue, Ph.D.[5]
Professor and Vice Chair
Department of Neuroscience
Wexner Medical Center
Ohio State University

Nicole Pukos, Rim Yoseph

It has been recognized since the 1970's that traumatic spinal cord injury induces acute demyelination of spared axons followed by remyelination. Our recent work examined what happens to oligodendrocyte replacement and changes in axons related to myelination beyond the first 2-3 weeks post-injury. Surprisingly, oligodendrocyte progenitors proliferate for over a month post-injury and associate with glutamatergic spinal axons. Oligodendrocyte genesis continues for at least 3 months post-injury and new oligodendrocytes myelinate spinal axons in this chronic setting. However, new data show that despite this ongoing endogenous repair response, significant axon pathology exists for at least 6 months post-injury, including loss of contacts by progenitor cells and significant spreading of nodal proteins. Thus, finding ways to improve engagement of oligodendrocyte lineage cells with spared axons may provide a therapeutic option for chronic spinal cord injury.

[5]Dr. McTigue received her undergraduate degree from Pennsylvania State University in Biology/Physiology in 1989, and then attended graduate school at Ohio State University, where she graduated with a Ph.D. in Physiology in 1995. She completed a postdoctoral fellowship in spinal cord injury (SCI) and then obtained a faculty position in the Department of Neuroscience in 2003, where she is currently a Professor and Vice Chair for Research. Her laboratory focuses on endogenous repair mechanisms within the spinal cord after injury with a focus on gliogenesis and long-term white matter changes. They also have an exciting newer line of research examining systemic metabolic problems and liver pathology arising as a result of SCI.

(F2) IN VIVO IMAGING OF CELLULAR DYNAMICS AND NEURAL ACTIVITY IN THE SPINAL CORD OF MICE
10:05AM-10:30AM

Chris B. Schaffer, Ph.D.
Cornell University

The technology for directly imaging the spatio-temporal patterns of neural activity in the rodent cortex has advanced dramatically. Using two-photon excited fluorescence microscopy, micrometer resolved, three-dimensional imaging deep into scattering tissue is possible. When combined with genetically encoded fluorescent calcium indicators, which increase fluorescence efficiency when they bind the calcium that increases in concentration after an action potential, it is now possible to record from many hundreds of genetically-defined neurons simultaneously in the cortex of awake, head-fixed mice during complex behavioral tasks. Such experimental capabilities enable studies of the neural activity patterns that underlie normal function as well as

how those activity patterns are changes in disease models. While cortical imaging is advancing rapidly, capabilities in other areas of the central nervous system remain underdeveloped. Neurons in the spinal cord play a critical role in coordinating rhythmic movements, such as walking and running, in tactile sensation, and in pain. Capabilities to image spatio-temporal patterns of neural activity in the spinal cord of mice could enable studies that uncover how spinal cord neural circuits accomplish these tasks, as well as how that function is impacted in disease models, such as after spinal cord injury. Several years ago, we developed an implantable chamber that provides long-term optical access to the dorsal spinal cord in mice, while causing minimal trauma to the spinal cord and minimally impacting locomotor function. We used this imaging chamber, in combination with two-photon excited fluorescence microscopy, we studied the increase in density of inflammatory cells and the heterogeneity of axon dieback near a minor spinal cord injury. Unfortunately, the dense myelination of the white matter on the dorsal surface of the spinal cord is highly optically scattering and prevents imaging of cells or other tissue structures in the deeper-lying grey matter using two photon imaging. Three-photon excited fluorescence microscopy has recently been shown to enable deeper imaging into scattering tissue than two-photon excitation. In the spinal cord, we have found that three-photon imaging enables imaging of cell and tissue structure to a depth of ~500 µm in the mouse spinal cord, as compared to ~150 µm using two photon excitation. We have further recorded the change in fluorescence associated with firing in neurons expressing the genetically-encoded calcium indicator, GCaMP6. For studies that link such neural activity to behavior, animal preparations and experimental setups are needed that enable neural activity to be imaged while the animal is awake and performing a behavioral task. For spinal cord imaging, we have shown we can train animals to stand and "move" on a treadmill while being held spine fixed by the implanted imaging chamber under the microscope. We found that with this setup, motion artifact was modest, just a few micrometers, and did not prevent imaging with sub-cellular resolution. Tracking of hindlimb motion in mice that were spine fixed and free running showed grossly similar limb movements, but with some noted shifts in the timing and relative amplitude of different phases of the gait cycle when spine fixed. Taken together, we have developed a suite of tools to enable the activity patterns of genetically-defined populations of spinal cord neurons to be imaged while mice are locomoting on a treadmill.

Looking forward, we intend to use this capability to study how activity in neurons that form the central pattern generator circuits shape limb motion. Previous work has identified key genetically-defined populations of neurons in these circuits and defined much of their connectivity. There have not been experimental tools that enable the spatio-temporal patterns of activity in these circuits to be correlated to the detailed kinematics of limb motion, however. Beginning with chx10-expressing excitatory interneurons, called V2a neurons, we aim to explicitly measure such correlations and study how neural activity patterns change with gait speed, etc. After incomplete spinal cord injuries, patients often experience spasticity in limb motion. We aim to examine the changes in neural activity that uncover such spasticity after a spinal cord injury decreases or eliminates the descending input from the brain to these central pattern generator circuits. Developing an understanding of the alterations of neural activity patterns that result from spinal cord injuries could open the door to new therapeutic approaches aimed at regularizing that neural activity with targeted drugs or implanted medical devices.

(F3) SYSTEMIC IMMUNE CHANGES AFTER SPINAL CORD INJURY
10:30AM-10:55AM

Ona E. Bloom, Ph.D.
The Feinstein Institute for Medical Research

Despite advances in medical care, life expectancy for persons with traumatic spinal cord injury (SCI) has not improved since the 1980s and remains lower than able-bodied persons. Infections are the leading cause of death for this population. Along with increased infection rates, inflammation is commonly observed in persons with SCI, where it may impede neurological recovery and promote many common medical consequences of SCI. These include elevated risk of cardiovascular disease, impaired wound healing, diabetes and neuropathic pain. Therefore, the major goal of my lab is to improve our

understanding of immune responses and related factors that influence neurological recovery, overall health and quality of life in persons with SCI.

Data will be presented from ongoing projects including: (1) "Biomarkers of Spontaneous Recovery from Traumatic SCI," (2) "Biomarkers in Pediatric Spinal Cord Injury/Abnormalities," (3) "Strive for Wellness Program Research Outcomes," (4) Contributions of Inflammatory Mediators in Chronic SCI and (5) Impact of exoskeletal-assisted walking on the immune systems of persons with chronic SCI.

The learning objectives for the audience are to increase understanding of:
(1) Systemic inflammation in individuals with acute or chronic traumatic SCI and the potential relationship to functional recovery
(2) Other aspects of immune system dysregulation after SCI and the relationship to overall health

(G) TRANSLATIONAL ISSUES
11:05AM-1:00PM
Chair: Adam B. Stein, M.D., Donald and Barbara Zucker School of Medicine at Hofstra Northwell

(G1) BENCH TO BEDSIDE AND BACK: TRANSLATIONAL RESEARCH IN ACUTE SPINAL CORD INJURY
11:05AM-11:55AM

Brian K. Kwon, M.D., Ph.D., FRCSC[6]
Canada Research Chair in Spinal Cord Injury
Dvorak Chair in Spinal Trauma
Professor, Department of Orthopaedics, University of British Columbia
International Collaboration on Repair Discoveries (ICORD)

The term "translational research" is frequently invoked as a desirable/necessary endeavour to bring effective therapies to fruition in biomedical research. But what is translational research? Why has it failed to deliver such effective therapies in so many areas of medicine, including spinal cord injury? And, what role can front-line clinicians play in translational research?

Here we use the backdrop of acute spinal cord injury to provide a perspective on the bidirectional flow of investigation and knowledge generation from both bench to bedside and bedside back to bench. We will describe the role of the descriptive characterization of biological responses in human SCI, and how this sheds light on clinically measurable pathophysiology. We will provide examples of how the study of human SCI can drive scientific investigations in the laboratory in a "bedside back to bench" approach. And we will describe how a large animal model can be used as an intermediary between typical rodent models and the human condition to promote bench to bedside translation.

[6]Dr. Kwon is a Professor in the Department of Orthopaedics at the University of British Columbia, the Canada Research Chair in Spinal Cord Injury, and holds the Dvorak Chair in Spine Trauma. He is an attending spine surgeon at Vancouver General Hospital, a level 1 trauma center and regional referral center for spinal cord injuries (SCI). He is also a research scientist at the International Collaboration on Repair Discoveries (ICORD) and the Chair of the SCI Cure Committee for the Rick Hansen Institute. His primary clinical and scientific research focus is in spine trauma and spinal cord injury. As a surgeon-scientist, he is particularly interested in the bi-directional process of translational research for spinal cord injury. He has worked extensively on establishing biomarkers of human SCI to understand the biology of human injury and to better stratify injury severity and improve the prediction of neurologic outcome. Dr. Kwon has led the development of a novel large animal model of SCI and is utilizing this for both bench-to-bedside and bedside-back-to-bench translational

studies. He has also led initiatives to establish a framework for how promising therapies for SCI should be evaluated in the laboratory setting prior to translation into human patients.

(G2) NEURAL BYPASS TECHNOLOGY FOR RESTORING FUNCTIONAL HAND MOVEMENT IN TETRAPLEGIA
11:55AM-12:25PM

Chad Bouton, M.S.[7]
Vice President, Advanced Engineering
Managing Director, Center for Bioelectronic Medicine
Division Leader, Neurotechnology and Analytics
Contributing Editor, Bioelectronic Medicine
The Feinstein Institute for Medical Research at Northwell Health

Millions suffer from diseases and injuries that lead to paralysis through disruption of signal pathways between the brain and the muscles. Bioelectronic devices are designed to restore lost function and can be used to form an electronic 'neural bypass' to circumvent disconnected pathways in the nervous system. Intracortically-recorded signals have been decoded to produce information related to motion allowing non-human primates and paralyzed humans to control computers and robotic arms through imagined movements. In a first-in-human clinical study, it has been shown that intracortically-recorded signals can be linked in real-time to muscle activation to restore movement in a paralyzed human. Machine-learning algorithms were developed to decode the neuronal activity and control electrical stimulation of the participant's forearm muscles through a custom-built high-resolution neuromuscular electrical stimulation system. The system allowed the participant to achieve isolated finger movements and continuous cortical control of six different wrist and hand motions. Furthermore, the participant completed functional tasks relevant to daily living. Clinical assessment showed that when using the system, the participant's motor impairment level improved from C5-C6 to a C7-T1 level unilaterally, giving him the critical abilities to grasp, manipulate and release objects. This was the first demonstration of successful control of muscle contraction utilizing intracortically-recorded signals in a paralyzed human. These results have significant implications in advancing bioelectronic technology for the millions of people worldwide living with paralysis. Future work will include developing improved machine learning algorithms and high-resolution implantable neural interface technology to support highly dexterous movement in the hand and movement in the lower extremities. Also, decoding methods are being developed for peripheral nervous system signals for extraction of important biomarkers for the diagnosis and treatment of a wide variety of diseases and conditions.

[7]Professor Chad Bouton is the VP of Advanced Engineering and the Director of the Center for Bioelectronic Medicine at The Feinstein Institute for Medical Research, the research arm of the Northwell Health System in New York.

Professor Bouton formerly served as research leader at Battelle Memorial Institute—the world's largest independent research and development organization—where he spent 18 years researching and developing biomedical technology. At the Feinstein Institute, he is performing ground-breaking research in neurotechnology to treat paralysis and is developing new technologies to accelerate the field of bioelectronic medicine.

Professor Bouton's pioneering work, allowing a paralyzed person for the first time to regain movement using a brain implant, has been featured on 60 Minutes, CBS, and presented at TEDx. He holds over 70 patents worldwide; his technologies have been awarded three R&D 100 Awards and he was recognized by the US Congress for his work in the medical device field. He has been named Inventor of the Year and Distinguished

Inventor by Battelle and was selected by the National Academy of Engineering in 2011 to attend the Frontiers in Engineering Symposium.

(G3) ROBOTICS TO RESTORE AND RETRAIN HUMAN MOVEMENTS
12:25PM-12:50PM

Sunil Agrawal, Ph.D.
Columbia University

Neural disorders or traumatic injury limit the ability of humans to perform activities of daily living. Robotics can be used to probe the human neuromuscular system and create new pathways to relearn, restore, and improve functional movements. Dr. Agrawal's group at Columbia University Robotics and Rehabilitation (ROAR) Laboratory has designed innovative robots for this purpose and tested these on a range of patients with deficits in balance and gait. The talk will highlight these scientific studies and also discuss how these could be extended to patients with spinal cord injury.

(G4) FUNCTIONAL OUTCOME CHANGES AFTER EXOSKELETAL-ASSISTED WALKING DURING ACUTE SCI INPATIENT REHABILITATION: A PILOT STUDY
12:50PM-1:00PM

Chung-Ying Tsai, Ph.D.
Icahn School of Medicine at Mount Sinai

Andrew D. Delgado, William J. Weinrauch, Nickolas A. Manente, Miguel X. Escalon, Thomas N. Bryce, and Ann M. Spungen

The purpose of this pilot study was to determine if incorporating exoskeletal-assisted walking (EAW) during inpatient standard of care rehabilitation therapy (SOC-EAW) could improve functional and motor recovery for people with acute/subacute spinal cord injury (SCI) compared with standard of care (SOC) rehabilitation therapy.

Design: A quasi-experimental design with a prospective intervention (SOC-EAW) group and a retrospective control (SOC) group was employed.

Setting: The study was conducted at a New York City hospital with an acute inpatient rehabilitation unit and SCI Model System of care.

Participants: Six people with SCI who were admitted to the acute inpatient rehabilitation unit during 2017 and were eligible for locomotor training as part of inpatient rehabilitation therapy were studied. The retrospective control group included twelve people with SCI who were admitted to the acute inpatient rehabilitation unit in 2016 and 2017 and were age-, gender-, ASIA Impairment Scale- and neurological level of injury-matched with the individuals in the intervention group using a 2:1 matching design. The individuals in the control group were selected through medical chart review by a research assistant who was blind to the study intervention group except for the matching characteristics of age, gender, ASIA Impairment Scale and neurological level of injury.

Intervention: In the intervention group, participants received locomotor training with an Ekso™ powered exoskeleton, incorporated into SOC three-hour per day duration inpatient therapies. In the retrospective

control group, participants received SOC three-hour per day duration inpatient therapies without use of a powered exoskeleton. The two groups had equal total therapy time per day.

Main Outcome Measures: Participants' functional activities were assessed using the Functional Independence Measure (FIM) by clinicians who were not part of the intervention. Upper and lower extremity motor scores (UEMS & LEMS), part of the International Standard for Neurological Classification of Spinal Cord Injury (ISNCSCI), were also assessed and recorded. All outcome measurements were performed at admission and discharge in both groups.

Results: By discharge, the average UEMS, LEMS, and FIM changes were better in the intervention group than the control group. The average LEMS and FIM score changes at discharge were statistically higher in the intervention group (11.3±7.3 and 35.3±11.5) compared to the control group (3.1±4.9 and 22.3±12.9, P=0.01 and 0.05, respectively). UEMS changes were not significantly different between the two groups (intervention: 4.2±7.1; control: 1.4±3.6).

Conclusion: The preliminary results suggest that integrating EAW into acute SCI inpatient rehabilitation may facilitate functional and lower extremity motor recovery. Further study is needed.

A NOTE TO OUR POSTER PRESENTERS

Thank you for your poster abstract submission and participation in the NYS SCI Research Symposium. There will be two poster sessions to better accommodate the number of poster presenters.

- Poster Session 1: Odd numbered posters should be displayed throughout the day on Tuesday, October 16, presented during the evening reception from 5:30pm-7:30pm, and taken down immediately following the reception.

- Poster Session 2: Even numbered posters should be displayed throughout the day on Wednesday, October 17, presented during breakfast from 8:00am-9:15am, and taken down prior to adjournment.

These sessions will take place in the lobby outside of the Carson Family Auditorium. Presenters can set up their poster as early as 8am on the day of their scheduled session. Presenters should be stationed at their poster to discuss their content with attendees during the assigned session.

POSTER ASSIGNMENTS

(1) TASK LEVEL HIERARCHICAL SYSTEM FOR BCI-ENABLED SHARED AUTONOMY

(2) NEURALIZED-PLURIPOTENT STEM CELLS (NIPSCS) IMPLANTED IMMEDIATELY AFTER SPINAL CORD INJURY AND COMBINED WITH ELECTRO-MAGNETIC STIMULATION AND EXERCISE TRAINING IN RATS

(3) CORTICAL AND SPINAL NEURAL EXCITABILITY FOLLOWING TRANSSPINAL STIMULATION IN HUMANS

(4) CHRONIC THETA BURST STIMULATION OF RAT MOTOR CORTEX PROMOTES CORTICOSPINAL TRACT SYNAPSES AND PRODUCES DAILY CARRYOVER OF MUSCLE RESPONSE POTENTIATION

(5) PAIRED BRAIN AND SPINAL CORD STIMULATION STRENGTHEN SPARED SPINAL CIRCUITS AFTER INJURY

(6) LACK OF T CELL-MEDIATED IMMUNE FUNCTION AMPLIFIES BONE LOSS DURING EARLY STAGES OF SPINAL CORD INJURY

(7) DISPARITIES IN ASSISTIVE TECHNOLOGY USE AND DISPARITIES IN HEALTH-RELATED BEHAVIORS AND BELIEFS AMONG INDIVIDUALS WITH SPINAL CORD INJURY

(8) MOUSE MODEL OF CORTICOMOTONEURONAL CONNECTIONS

(9) NON-INVASIVE CERVICAL ROOT STIMULATION TO FACILITATE CORTICOSPINAL TRANSMISSION

(10) AAV VECTOR MEDIATED DELIVERY OF NG2 FUNCTION NEUTRALIZING ANTIBODY: NOVEL GENE THERAPY DESIGNED TO IMPROVE SYNAPTIC TRANSMISSION, LOCOMOTION AND URINARY TRACT FUNCTION AFTER MILD SPINAL CORD INJURY IN ADULT RATS

(11) SURFACE EMG-TRIGGERED CLOSED LOOP STIMULATION FOR INDIVIDUALS WITH SPINAL CORD INJURY: A CASE REPORT

(12) MODELING ALS DIFFERENTIAL VULNERABILITY USING ESC-DERIVED CRANIAL AND SPINAL MOTOR NEURONS

(13) PAIRED BRAIN AND SPINAL CORD STIMULATION AUGMENTS MUSCLE RESPONSES THROUGH CONVERGENCE OF THE CORTICOSPINAL TRACT AND LARGE DIAMETER AFFERENTS ON SPINAL INTERNEURONS

(14) MAKING FUNCTIONAL NEURONAL CIRCUITRY: INTERNEURON SPECIFICATION IN THE ZEBRAFISH SPINAL CORD

(15) DEVELOPMENT OF A PELVIC-ASSISTED STAIRMILL TRAINER

(16) INJURY-ACTIVATED MICROGLIA SHARE COMMON GENE SIGNATURES AND FUNCTIONAL PROFILES WITH DEGENERATION-ASSOCIATED MICROGLIA

(17) DEVELOPMENT OF A STAND TRAINER FOR SCI PATIENTS

(18) DELETION OF PLEXINB2 IMPAIRS SPINAL CORD INJURY REPAIR PROGRAM BY ALTERING MICROGLIA-ASTROCYTE COMMUNICATION

(19) IMPROVING LOCOMOTOR FUNCTION AFTER SPINAL CORD INJURY WITH A PERTURBATION-BASED BALANCE TRAINING

(20) PHARMACOLOGICAL TARGETING OF ION CHANNELS LEADS TO RAPID AND SUSTAINED BEHAVIORAL IMPROVEMENTS FOLLOWING SPINAL CORD INJURY

(21) TRAINING UPPER BODY USING A TRUNK SUPPORT TRAINER (TruST)

(22) A FIBROUS ESTROGEN POLY-PRODRUG SCAFFOLD TO MODULATE ASTROCYTE REACTIVITY

(23) WHEELCHAIR ROBOT FOR ACTIVE POSTURAL SUPPORT OF SCI PATIENTS (WRAPS)

(24) IDENTIFYING GENES AT THE CORE OF SUCCESSFUL RECOVERY FROM SCI USING *XENOPUS* FROGS

(25) CHRONIC ELECTRICAL STIMULATION OF THE CST SYSTEM LEADS TO REPAIR AND FUNCTIONAL RECOVERY AFTER SCI INJURY VIA REACTIVATION OF DEVELOPMENTALLY REGULATED MOLECULAR PATHWAYS

(26) ALPHA-TUBULIN ACETYLTRANSFERASE IS A NOVEL TARGET MEDIATING NEURITE GROWTH INHIBITORY EFFECTS OF CSPGS AND MAG

(27) PAIRED THERAPUETIC STIMULATION OF BRAIN AND SPINAL CORD IN A LARGE ANIMAL MODEL OF CERVICAL CONTUSION TO REHABILITATE UPPER-LIMB NEUROMODULATION

(28) PUM2 SHAPES THE AXONAL TRANSCRIPTOME THROUGH RETENTION OF TARGET MRNAS IN THE CELL BODY

(29) NONINVASIVE TRANSSPINAL STIMULATION PRODUCES MUSCLE ACTIVITY REVERSALS IN HEALTHY HUMANS DURING TREADMILL WALKING

(30) SIGNALING PATHWAYS TO REGENERATIVE REPAIR OF SPINAL CORD INJURY: AN INTEGRATIVE MODEL FOR PHARMACOLOGIC EXPLORATION

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(52) A DEVICE-ASSISTED SURGICAL PROCEDURE TO PROVIDE A CONTROLLED BIOPHYSICAL ENVIRONMENT FOR SPINAL CORD REGENERATION

(53) NEURAL STEM CELL AND NANOPARTICLE ENCAPSULATION IN MICRORIBBON HYDROGELS IN A TRANSPORTABLE PLATFORM FOR SPINAL CORD INJURY SITE MODULATION AND REPAIR

(1) TASK LEVEL HIERARCHICAL SYSTEM FOR BCI-ENABLED SHARED AUTONOMY

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We describe a novel hierarchical system for shared control of a humanoid robot. This system shows great potential for helping users with severe motor disabilities interact with a robotic assistant in Activities of Daily Life (ADL). Our framework uses a low-bandwidth Brain Computer Interface (BCI) to interpret electroencephalography (EEG) signals via Steady- State Visual Evoked Potentials (SSVEP). This BCI allows a user to reliably interact with the humanoid. Our system clearly delineates between autonomous robot operation and human- guided intervention and control. Our shared-control system leverages the ability of the robot to accomplish low level tasks on its own, while the user assists the robot with high level directions when needed. This partnership prevents fatigue of the human controller by not requiring continuous BCI control to accomplish tasks which can be automated. We have tested the system in simulation and in real physical settings with multiple subjects using a Fetch mobile manipulator. Working together, the robot and human controller were able to accomplish tasks such as navigation, pick and place, and table clean up. The framework presented can use different BCI techniques at different layers to get human input into a robotic system. As new and different BCI technologies are developed, they can be interchanged and adopted into different layers of the hierarchy.

Supported by SCIRB contract # DOH01-C30828GG-3450000

(2) NEURALIZED-PLURIPOTENT STEM CELLS (NIPSCS) IMPLANTED IMMEDIATELY AFTER SPINAL CORD INJURY AND COMBINED WITH ELECTRO-MAGNETIC STIMULATION AND EXERCISE TRAINING IN RATS

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Adult rats received T10 contusion SCI and were implanted with NiPSCs immediately after injury. Two groups were examined. Gr 1, received NiPSCs only. Gr 2, received NiPSCs and spinal electro-magnetic stimulation (SEMS) followed by treadmill exercise training, every other day (Mo, We, Fr) for 6 weeks. NiPSCs were derived from human fibroblasts, assessed for multipotency in the Horner lab and then live-shipped to the Arvanian lab. All rats received the immunosuppressant cyclosporine daily during a six week survival period to protect NiPSCs from immune-mediated rejection. Locomotion of all rats was assessed weekly using BBB scoring and Automated catwalk. At the end of a six-week post-operative survival period, motor-evoked potentials measured from the BF muscle and evoked by SEMS were examined to evaluate transmission at spino-muscular circuitry. After completion of behavioral and electrophysiology evaluations, the rats were perfused, spinal cords removed and cryosections were cut and prepared for immunochemistry evaluation. We used STEM 121 antibody to visualize presence of injected NiPSC's.. We also performed double staining with antibodies for oligodendrocytes and neurons to determine the fate of injected stem cells. We found that overall all rats exhibit no adverse effects from NiPSCs implantation. Animals that received NiPCSs combined with chronic SEMS/exercise treatment exhibited better recovery of locomotor function and transmission compared with rats that received NiPSCs only.

Effects were, however, less robust than expected. Importantly, the rate of behavioral recovery correlated with NiPSCs signal. We hypothesize that acute delivery of NiPSCs could have limited their function or engraftment due to the inflammatory and metabolic challenge. We anticipate that delayed implantation of NiPSCs, i.e. at 2 and 6 weeks post injury (when microglia/macrophage responses are attenuated) should be the next step and represents a better approach.

Supported by NYS DOH, CHN Foundation, VA Merit Award

(3) CORTICAL AND SPINAL NEURAL EXCITABILITY FOLLOWING TRANSSPINAL STIMULATION IN HUMANS

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In this study we sought to establish the effects of repetitive transspinal stimulation on cortical and spinal neural circuits in healthy individuals. Before and after 40-mins of repetitive cathodal transspinal stimulation at 0.2 Hz over the thoracolumbar enlargement, we assessed changes in cortically-induced indirect (I)-waves, transspinal evoked potential (TEP) amplitudes in response to muscle spindle afferent conditioning stimulation, and soleus H-reflex amplitudes in response to transspinal conditioning stimulation. For changes in I-waves, we examined changes in the right tibialis anterior (TA) MEP amplitudes evoked by paired-pulse TMS at interstimulus intervals (ISIs) ranging from 1.1 to 5.3 ms. To establish neural interactions between TEPs and muscle spindle afferents, we established amplitude changes in TEPs of bilateral ankle flexors/extensors following stimulation of the right soleus muscle spindle group Ia afferents, and right soleus H-reflexes following transspinal stimulation at numerous conditioning-test intervals ranging from minus to positive 100. Our findings indicate that 40-mins of repetitive transspinal stimulation significantly decreases paired-TMS evoked TA MEPs at ISIs of 1.3, 2.7, 3.5, 4.1, 4.7, and 5.3 ms, reflecting a depression in cortically-induced I-waves. Whilst significantly increasing TEP and soleus H-reflex depression in response to muscle spindle Ia afferent and transspinal conditioning stimulation, respectively, reflecting a potentiation of inhibition in spinal neural circuits, as well as afferent and motor fibers. Overall these results demonstrate an inhibition of cortical and spinal neural excitability in response to repetitive transspinal stimulation. Thus, this novel method may be used as a neuromodulation tool to normalize cortical and spinal neural excitability in neurological disorders.

Supported by The Craig H. Neilsen Foundation [Grant No. 339705] and the New York State Department of Health, Spinal Cord Injury Research Program [Contract No. C32095GG, C32248GG, C30836GG].

(4) CHRONIC THETA BURST STIMULATION OF RAT MOTOR CORTEX PROMOTES CORTICOSPINAL TRACT SYNAPSES AND PRODUCES DAILY CARRYOVER OF MUSCLE RESPONSE POTENTIATION

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While acute theta burst stimulation (TBS) of the motor cortex (MCX) can strengthen the cortical input to the spinal cord in humans and animals, the effects of chronic TBS are unclear. Importantly, chronic TBS has been used to improve motor function after SCI. Using a rat model, we aimed to determine if, after chronic iTBS: 1) there are structural changes in corticospinal tract (CST) synapses in the spinal cord; 2) motor evoked potentials (MEPs) are potentiated; and 3) there was a day-to-day carryover and buildup of EMG enhancement during the chronic stimulation period.

Naïve rats received 10 days of iTBS (27 minute per daily session). CST axons showed increased contralateral outgrowth after stimulation compared with controls. We used pre- and postsynaptic marker expression and 3D high-resolution reconstruction to assay structural changes. iTBS caused a significant increase in the number and volume of postsynaptic sites. These changes were paralleled by upregulation of the mTOR (Ps6) and Jak/STAT (PSTAT3) signaling following iTBS, using Western blotting and immunohistochemistry of layer 5 neurons.

Subsequently, we tested the effects of daily iTBS for 10 days on MEPs. One day of stimulation (27 minutes) augmented MEPs for 24-48 hours, indicating significant persistence. Each daily stimulation is comprised of 5 separate 190 second stimulation epochs. Interestingly, one stimulation epoch produced strong EMG potentiation for up to 45 minutes. Ten days of stimulation produced MEP enhancement that persisted for at least 10 additional days. These findings indicate within-session and daily across-session carryover of MEP enhancement.

We propose that each daily session of iTBS produces LTP of MCX-muscle connections. The LTP carries over daily sessions, suggesting a persistent plastic state that enables CST axonal outgrowth. Combined potentiation of connections, CST outgrowth, and increased CST postsynaptic sites demonstrate the potential utility of iTBS to strengthen spared motor circuits following injury.

Supported by NYS SCIRB (C30606GG-JM; C30860GG-AA) and NIH (5R01NS064004)

(5) PAIRED BRAIN AND SPINAL CORD STIMULATION STRENGTHEN SPARED SPINAL CIRCUITS AFTER INJURY

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Using the principles of associative learning, we have developed a neuromodulation paradigm that augments sensorimotor excitability in the spinal cord. We pair supra-threshold motor cortex stimulation with sub-threshold spinal cord stimulation using a timing that causes the stimuli to arrive synchronously in the spinal cord. In uninjured rats, when pairing is performed repeatedly for 5 minutes, there is a robust increase in motor evoked responses (MEPs) that lasts up to 2 hours. The present study tests the efficacy of paired stimulation in rats with cervical spinal cord injury (SCI). We hypothesized that the tissue spared by SCI would be sufficient to enable lasting effects of paired stimulation after a *single* session. We further hypothesized that *repeated* sessions of paired stimulation would produce cumulative effects on spinal excitability. We used three sets implantable electrodes: epidural cortical, biceps EMG, and spinal epidural electrodes. Biceps MEPs after cortical stimulation and forelimb H-reflexes were recorded. A moderate C4 contusion injury was performed, and electrode arrays were inserted over C5-C6. Two weeks later, repetitive stimulation was performed. We measured biceps MEPs produced by cortical and spinal cord stimulation. Both cortical and spinal MEPs were augmented by ~75% and this lasted for over 60 minutes. We also measured H-reflexes in the forelimb. Rats with SCI were hyperreflexic compared to their baseline, as demonstrated by the rate-dependent suppression of the H-reflex. Paired stimulation restored this measure of hyperreflexia close to the values of uninjured rats. Finally, we measured the effects of paired stimulation 5 minutes every day for 10 days in rats with a cut injury to the corticospinal tract from one hemisphere. Over the 10 days of pairing, the effects increased from ~75% change to more than 250%. This suggests that there can be a cumulative effect of repeated pairing after injury. Thus, the circuits spared by CST lesions were sufficient to augment MEPs with paired stimulation while decreasing hyperreflexia.

Supported by the Travis Roy Foundation to Cure Spinal Cord Injury

(6) LACK OF T CELL-MEDIATED IMMUNE FUNCTION AMPLIFIES BONE LOSS DURING EARLY STAGES OF SPINAL CORD INJURY

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Patients with spinal cord injury (SCI) invariably suffer from severe sub-lesional bone loss that is resistant to treatment, thus, better understanding of the underlying mechanisms is indicated.

Whether T cell-mediated immune function influences SCI-induced bone loss is unknown. Therefore, T cell-deficient (TCR beta -/-) male mice were reconstituted or not with T cells for 4 weeks before animals underwent sham or contusion SCI surgery and followed for 1 week. Bones were evaluated by micro-computed tomography scanning (micro-CT). Sera were collected and levels of bone turnover markers and factors were measured by ELISA. The micro-CT analysis revealed a marked reduction in both femur and tibia trabecular fractional bone volume in all SCI animals compared to sham animals. Strikingly, the magnitude of loss in bone volume was more pronounced in SCI T cell-deficient than in T cell-reconstituted animals (*P=0.02*). Additionally, an equal decrease in trabecular thickness was observed in all SCI animals. Other structural indices of bone strength, namely trabecular connectivity and three-dimensional structure model index was not significantly different in any group. Analysis of bone mid-shaft region showed no difference in cortical thickness or porosity among the groups. Interestingly, the biochemical analysis demonstrated that the serum levels of P1NP, a bone formation marker, were significantly lower in SCI T cell-reconstituted than in SCI T cell-deficient animals (*P*=0.03). Conversely, the serum levels of CTX, a bone resorption marker, were significantly elevated in SCI T cell-deficient animals but not in SCI T cell-reconstituted animals (*P*=0.03). Serum levels of IGF-1 and RANKL/OPG ratio were lower, while sclerostin levels were higher, in SCI than in sham groups. Collectively, these results demonstrate that T cells distinctly alter bone turnover and microarchitecture during early stages of SCI. The findings suggest that modulating immune function could minimize bone loss and lower fragility fractures during early stages of SCI.

Supported by SCIRB contract # C32093GG

(7) DISPARITIES IN ASSISTIVE TECHNOLOGY USE AND DISPARITIES IN HEALTH-RELATED BEHAVIORS AND BELIEFS AMONG INDIVIDUALS WITH SPINAL CORD INJURY

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Objective: To assess assistive technology (AT) use and health-related behaviors/beliefs (HRBBs) among individuals with spinal cord injury (SCI). To identify any disparities in AT use and HRBBs between various sociodemographic groups within this population.

Methods: This was a cross-sectional study involving 15 SCI Model Systems (SCIMS) centers throughout the U.S. that collected data on AT use (eg. e-mail/internet use, computer use, cellphone ownership). A subset of 8 centers collected further data with a standard questionnaire asking participants how much they agree/disagree with common HRBBs (eg. “I am directly responsible for my health related to my SCI.”; “Luck plays a big part in how my health improves.”). Participant demographics and SCI related information were pulled from the SCIMS database.

Results: Participants included 1145 individuals: predominantly male (78.0%), white (77.3%), mean age 46.4 years (SD=15.2). HRBB data were from a participant subset of 738 individuals: again predominantly male (77.1%), white (76.4%), mean age 45.8 years (SD=15.4). AT data showed older participants were less likely to access e-mail/internet (p=0.01), use computers

(p<0.0001), or own cellphones (p<0.0001). White participants had higher computer (p<0.0001) and e-mail/internet use (p<0.05) than non-white participants. HRBB data showed older participants were less likely to attribute their condition to their own behaviors (p values ranging from <0.001 to p=0.076) but also less likely to attribute their condition to luck/fate (p from <0.05 to <0.001). White participants were less likely to attribute their condition to luck/fate (p from <0.01 to p=0.63) than non-white participants.

Conclusions: Results from our studied sample suggest that despite the variety of AT made available to date, sociodemographic disparities still limit its usefulness to some individuals with SCI. It is possible that differences in HRBBs are related. Future studies should investigate the relationship between disparities in HRBBs and disparities in AT use.

Supported by the National Institute on Disability Independent Living and Rehabilitation Research SCIMS grants

(8) MOUSE MODEL OF CORTICOMOTONEURONAL CONNECTIONS

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Spinal cord iunjury (SCI) damages corticospinal tract (CST) connections that link the brain with spinal cord motor circuits. A key feature of the human CST is the direct/monosynaptic connection between the CST and motoneurons, termed corticomotoneuronal (CM) connections. Significant CM connections are absent in rodents, the principal animal species for modeling SCI. We recently developed a mouse model of CM connections, by conditional forebrain deletion of the gene for the guidance molecule PlexinA1 [PlexinA1f/f; Emx1-Cre mice (PlxA1KO)]. We are using this model to study the impact of CM connections on functional changes after injury. Here we examined the properties of these CM connections to further our understanding of their function and to provide a baseline for on-going SCI studies. To assay CM connections, we used stimulus triggered EMG averaging (StTA) in response to single-pulse motor cortex or CST stimulation. This is an electrophysiological technique that demonstrated CM connections in primates. StTA in monkeys reveals short-latency EMG facilitation (post-stimulus facilitation; PStF) in individual muscles and typically EMG suppression (post stimulus suppression; PStS). Intracellular recording studies in monkeys show that PStF and PStS are associated with monosynaptic motoneuronal depolarization and oligosynaptic hyperpolarization, respectively. We examined both motor evoked potentials (MEP) and single motor units (MU). StTA in PlxA1KO mice, compared to PlxA1f/f controls, produces significantly shorter latency PStF, faster peak EMG response recruitment, and shorter-duration (phasic) responses. Similar to the primate, PStF was followed by shorter latency, larger, and longer duration PStS in the PlxA1KOs than controls. Similar results were obtained for MEPs and MUs. Experiments are in progress to elucidate differences in CM projections to multiple muscles. Short-latency phasic responses in the PlxA1KO that are tightly linked to robust EMG suppression, is a way to ensure the occurrence of a temporally-focused and spatially-fractionated motor response evoked by cortical descending signals.

Supported by NIH (5R01NS079569-JHM; Craig H Neilsen Foundation-JHM)

(9) NON-INVASIVE CERVICAL ROOT STIMULATION TO FACILITATE CORTICOSPINAL TRANSMISSION

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Background: Most spinal cord injuries (SCI) spare some neural tissue. Activating spared nerve circuits augments neural plasticity. With this goal in mind, we aim to use a novel method of non-invasive cervical electrical stimulation (CES). CES activates nerve roots across multiple myotomes in both upper extremities simultaneously. To understand CES circuit interactions, we measured the effects of CES delivered alone or paired with transcranial magnetic stimulation (TMS) or peripheral nerve stimulation (PNS).

Methods: Transcutaneous stimulation is delivered via 5x10 cm electrodes placed over the C4-C5 levels anteriorly and T2-T4 levels posteriorly. Preliminary experiments involved optimizing CES waveform and characterizing transmission routes. Subsequent experiments are measuring electromyographic responses of hand muscles to CES paired with TMS or PNS at varying intensities and timing. Safety is monitored via blood pressure, heart rate, oxygenation, vital capacity, and subjective tolerance.

Results: Across ongoing studies, 22 able-bodied volunteers, 15 incomplete cervical SCI subjects, and 11 amyotrophic lateral sclerosis subjects have undergone >225 CES sessions without major safety or tolerability issues. A cathode-posterior, 2 ms biphasic waveform was determined to provide optimal stimulation characteristics. Double CES pulses delivered at 40 ms apart showed that at peri-threshold intensity, CES activates sensory afferents susceptible to homosynaptic depression. At higher intensities, CES activates motor efferents not susceptible to homosynaptic depression. Sub-threshold CES pulses facilitate single TMS-evoked potentials in timing-dependent fashion. Repeated combinations of CES or PNS with TMS over 20 minutes have not shown consistent effects. Other experimental analyses are ongoing.

Discussion: Our novel approach to transcutaneous cervical electrical stimulation provides both mechanistic insight and potential therapeutic application toward upper extremity muscles after SCI. The ability of sub-threshold CES to facilitate response to transcranial magnetic stimulation raises the possibility that it may also be able to enhance responses to physical rehabilitation by facilitating volitional movements.

Supported by SCIRB contract # C30599GG

(10) AAV VECTOR MEDIATED DELIVERY OF NG2 FUNCTION NEUTRALIZING ANTIBODY: NOVEL GENE THERAPY DESIGNED TO IMPROVE SYNAPTIC TRANSMISSION, LOCOMOTION AND URINARY TRACT FUNCTION AFTER MILD SPINAL CORD INJURY IN ADULT RATS

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NG2 proteoglycan is considered one of the key inhibitory factors that restrict growth and plasticity in damaged CNS and is the major part of the glial scar formed following spinal cord injuries (SCI). In our previous studies we have demonstrated beneficial effects of neutralization of NG2 proteoglycan using monoclonal antibodies against it on synaptic and anatomical plasticity as well as locomotor function after hemisection SCI. Currently we have developed a novel gene therapy tool for prolonged and clinically-relevant delivery of a recombinant single chain variable fragment (scFv) anti-NG2 antibody. In this study we have examined effects of AAV-NG2Ab alone or in combination with AAV-NT3 in adult rats with thoracic T10 SCI, using both mild (150 kdyn) and severe (250 kdyn) contusion models. Four groups of animals were examined where AAV vectors were injected immediately after the injury expressing GFP, NG2-Ab, NT-3 or combination of NG2-Ab and NT-3 together. Battery of behavioral tests was used to evaluate sensory and motor function recovery. In-vivo singe cell electrophysiological recording from lumbar spinal cord was used to evaluate synaptic transmission. Lower urinary tract function was assessed during the survival period using metabolic chambers to evaluate urine production. Terminal cystometry/electrophysiology with simultaneous acquisition of external urethral sphincter EMG activity and bladder pressure was used to evaluate bladder function. In case of mild (150 kdyn) contusion SCI, both the AAV-NG2Ab and AAV-NG2Ab combined with AAV-NT3 treatment groups demonstrated significant improvements in locomotor function compared to control treated group. Treatment also induced improvements of bladder function. The best recovery of locomotion and lower urinary tract function was observed in the group that received combinational treatment. No significant improvements were observed in case of severe (250 kdyn) contusion. Results suggest that proposing gene therapy may be an effective approach for improving function after mild SCI, by improving transmission through the anatomically intact surviving axons. However this treatment is not sufficient to improve function in case of severe SCI, when there is limited or no fibers spanning SCI epicenter.

Supported by NYS DOH, CHN Foundation, VA Merit Award

(11) SURFACE EMG-TRIGGERED CLOSED LOOP STIMULATION FOR INDIVIDUALS WITH SPINAL CORD INJURY: A CASE REPORT.

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Background: Non-invasive paired stimulation via transcranial magnetic stimulation (TMS) over motor cortex and electrical stimulation (PNS) over a peripheral nerve has been demonstrated to enhance synaptic transmission after spinal cord injury (SCI). Additionally, utilizing subjects' endogenous signals to trigger stimulation (closed loop stimulation) has shown greater motor recovery compared to open-loop stimulation in an incomplete SCI rat model. Therefore, we have developed an EMG-triggered closed-loop non-invasive stimulation system to improve hand functions for humans with cervical SCI. We report the preliminary results from one chronic cervical SCI participant.

Methods: To date, one 56 y/o male with chronic C4 neurological level SCI (ASIA Impairment Scale C) has completed testing and analysis. TMS was targeted at the hand M1 and PNS was delivered over the median nerve at the wrist to target C8-T1 spinal synapses. Abductor pollicis brevis (APB) muscle EMG activity (15% maximal voluntary contraction) was used to trigger the stimulation devices. Five 20-minute sessions at 0.1 Hz were conducted: EMG-triggered TMS, EMG-triggered PNS, EMG-triggered paired stimulation, passive paired stimulation, and hand movement without stimulation. Our primary outcome is Peak-to-Peak Amplitude of APB Motor Evoked Potentials at 120% intensity of Resting Motor Threshold (MEP_{120}) during the 60 minutes after each stimulation session.

Results: Relative to baseline, the most improvement of MEP_{120} after the stimulation session was hand movement without stimulation (+ 204.13±121.10%), followed by passive paired stimulation (+91±75.15%) and EMG-triggered PNS (+96.37±75.90). The MEP_{120} slightly decreased after EMG-triggered TMS (-39.17±18.30) and EMG-triggered paired stimulation (-29.00±27.61).

Discussion: Interestingly, the preliminary data from one subject suggests that EMG-triggered cortical stimulation decreased the MEP_{120} compared to passive stimulation or EMG-triggered peripheral nerve stimulation. The findings might indicate the importance of stimulation delivery timing and possible interference between external stimulation and endogenous signals that travel over the corticospinal pathway. Experiments are ongoing with more subjects.

Supported by SCIRB contract # C32629GG

(12) MODELING ALS DIFFERENTIAL VULNERABILITY USING ESC-DERIVED CRANIAL AND SPINAL MOTOR NEURONS

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In amyotrophic lateral sclerosis (ALS) spinal motor neurons (SpMN) progressively degenerate while a subset of cranial motor neurons (CrMN) are spared until late stages of the disease. Understanding the nature of CrMN resistance to ALS will help to improve understanding of ALS pathology and inspire effective therapeutic strategies. Using a rapid and efficient mouse embryonic stem cells (ESC) to SpMNs and CrMNs differentiation protocol, we now report that ESC-derived CrMNs accumulate less human (h) SOD1 and insoluble p62 than SpMNs over time. ESC-derived CrMNs rely more on the ubiquitin proteasome system to degrade misfolded proteins and are intrinsically more resistant than SpMNs to chemically-induced proteostatic stress. Moreover, chemical activation of the proteasome rescues the SpMN sensitivity to proteostatic stress. Confirming the validity of this ESC-based model, ALS-resistant CrMNs accumulate less insoluble hSOD1 and p62-containing inclusions than SpMNs in the hSOD1 G93A mouse model and primary ALS-resistant CrMNs are also more resistant than SpMNs to proteostatic stress. Together, these results establish an ESC-based platform to study differential ALS vulnerability and identify the greater capacity to maintain a healthier proteome a possible mechanism to resist ALS-induced neurodegeneration.

Supported by SCIRB contract # DOH01-C32243GG-3450000

(13) PAIRED BRAIN AND SPINAL CORD STIMULATION AUGMENTS MUSCLE RESPONSES THROUGH CONVERGENCE OF THE CORTICOSPINAL TRACT AND LARGE DIAMETER AFFERENTS ON SPINAL INTERNEURONS

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We have developed a neuromodulation paradigm that pairs stimulation of motor cortex and dorsal spinal cord to strengthen spared neural circuits after spinal cord injury. Sub-threshold spinal cord stimulation strongly augmented cortical motor evoked potentials (MEPs) when they arrive synchronously in the spinal cord. However, the circuit-level mechanism of the augmentation has not been determined. We hypothesized that the corticospinal tract (CST) and large diameter afferents converge onto premotor spinal interneurons during paired stimulation. To test our hypothesis, we selectively inactivated each of these circuits with a chemogenetic method (Designer Receptor Exclusively Activated by Designer Drug, DREADD) during paired stimulation. For CST inactivation, we injected an AAV1 into the forelimb area of a motor cortex and an AAV-retro into the cervical spinal cord; doubly infected corticospinal neurons express an inhibitory DREADD. For inactivation of large diameter afferents, we injected AAV5 into cervical dorsal root ganglia; the tropism of this virus is for large-diameter neurons. When the CST was inactivated with the designer drug, clozapine N-oxide (CNO), the number of paw adjustment in pasta manipulation test was decreased and the MEPs augmentation was abolished in the targeted forelimb. Inactivation of large diameter afferents also abolished the MEPs augmentation in the targeted forelimb. In both cases, paired stimulation effects returned when CNO washed out. In addition, interneurons were activated after repeated paired stimulation in the deep dorsal horn and medial intermediate zone where the CST axon and large diameter afferents overlap. Thus, we demonstrate that the CST and large diameter afferents are necessary for the effects of paired stimulation, and the site of their convergence is likely interneurons in the deep dorsal horn and

medial intermediate zone. Understanding the systems-level mechanisms of paired stimulation could help to improve its targeting and efficacy for restoring function after injury.

(14) MAKING FUNCTIONAL NEURONAL CIRCUITRY: INTERNEURON SPECIFICATION IN THE ZEBRAFISH SPINAL CORD.

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Spinal cord damage caused by abnormal development, injury or disease profoundly impacts quality of life, but strategies to repair damaged sites remain elusive. To develop more effective treatments, it is essential that we understand the molecular mechanisms that regulate development of functional spinal neuronal circuitry.

Specification of distinct neurons with particular functional properties is a crucial step in circuit formation. Interneurons constitute most of the neurons in the spinal cord and they function in almost all neuronal circuits. However, there are significant gaps in our knowledge of how spinal interneurons with specific functional characteristics develop. All the data so far, suggest that properties of distinct interneurons are determined by the transcription factors these cells express as they start to differentiate. However, in many cases, it is still unclear which transcription factors specify particular properties.

To address this critical gap in knowledge we have identified transcription factors that are strong candidates for specifying particular interneuron properties and we are testing the functions of these proteins. Notably, we have already identified several families of transcription factors that are required to specify and/or maintain the neurotransmitter properties of particular spinal interneurons. For example, we have shown that Pax2 and Pax8 are required for the inhibitory fates of many distinct spinal neurons, Evx1, Evx2, Lmx1a and Lmx1b are required for the excitatory fates of V0v neurons and Gata2a, Gata3 and Tal1 are required for the inhibitory fates of V2b spinal neurons. Current work is investigating the functions of additional transcription factors and the molecular mechanisms though which they act.

Our ultimate aims are to identify the complete complement of transcription factors expressed by each of the different classes of spinal interneurons and to determine how these proteins regulate the distinct functional characteristics of these cells and hence the properties of resulting neuronal circuitry.

Supported by SCIRB contract # C32253GG

(15) DEVELOPMENT OF A PELVIC-ASSISTED STAIRMILL TRAINER

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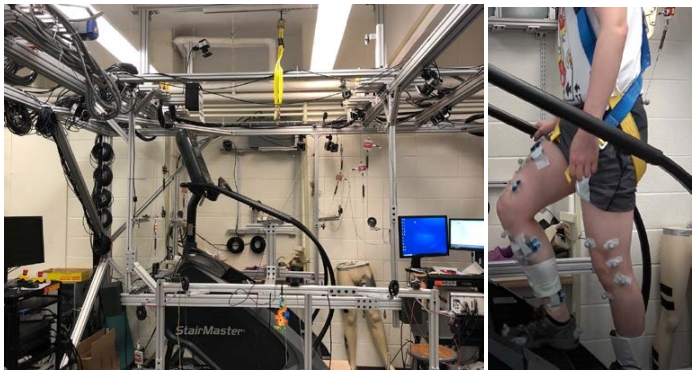

A pelvic-assisted stair-trainer developed at Columbia ROAR lab

Stair climbing is a common and frequent dynamic activity in daily life. It is physically demanding and biomechanically challenging. This task becomes even more challenging in the presence of muscle weakness and incoordination, such as in spinal cord injury. This study is aimed to: (1) characterize the biomechanics of stair climbing, i.e., kinematics, kinetics, muscle activity, and metabolic in both able-bodied individuals and those with gait impairments; (2) investigate how active assistance can be provided at the pelvis by a novel Tethered Pelvic Assist Device (TPAD) to assist and train stair climbing.

The system consists of a powered stair-mill, a motion capture system to record kinematics of the lower body and the trunk while walking on the stair-mill. Eight AC motors are placed above the stair-mill to form a tethered pelvic assist system which control the tension the wires connected to a pelvic brace. The tensions in the wires are regulated to apply a given force and moment on the pelvis, based on the human motion sensed by the motion capture system. Preliminary experiments will be presented that characterize human movements on the stairs, with and without the assistance of pelvic device.

Supported by SCIRB contract # C32238GG

(16) INJURY-ACTIVATED MICROGLIA SHARE COMMON GENE SIGNATURES AND FUNCTIONAL PROFILES WITH DEGENERATION-ASSOCIATED MICROGLIA

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Prolonged neuroinflammation is thought to contribute to poor neurological recovery after CNS injury, yet molecular signatures and functional profiles of activated microglia in injury settings remain unclear. Here, we using cell type-specific nuclei purification we generated comprehensive temporal transcriptomic maps of injury-activated microglia/macrophages (IAM) after spinal cord injury. We highlighted a core IAM gene program that comprises immunity, lipid metabolism, and scavenging. We also detected a transcriptionally distinct, progressive IAM activation that encompasses regulation of proliferation and motility at early stage, axon chemoattraction and ion channel activity at intermediate stage, and matrix re-organization at late stage. Remarkably, anti-inflammatory gene sets were enriched in IAM. We also saw a large overlap between IAM and degeneration-associated microglia (DAM) gene signatures involved in debris clearing, matrix organization and secreted factors. Finally, transcriptional changes in IAM were paralleled with

alternative splicing. These findings suggest common functional profiles of innate immunity in post-traumatic injury and neurodegeneration.

(17) DEVELOPMENT OF A STAND TRAINER FOR SCI PATIENTS

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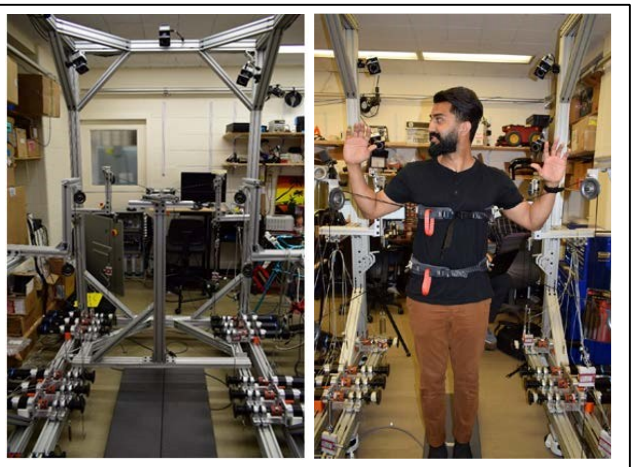

Figure: Thestand trainer design and a subject performing experiments in the trainer.

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 assists a subject at the pelvis, trunk, and the knees. The stand trainer is designed to (i) provide assistance as needed for balance of 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 cablebased 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 servomotor and the controller uses the real-time data from a motion capture system for closed-loop control. Preliminary experiments will be presented to show the capability of the system and plans to examine the effectiveness of robot-assisted stand training in the improvement of postural control in spinal cord injured individuals who are unable to stand independently.

Supported by SCIRB contract # C31290GG

(18) DELETION OF PLEXINB2 IMPAIRS SPINAL CORD INJURY REPAIR PROGRAM BY ALTERING MICROGLIA-ASTROCYTE COMMUNICATION

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Semaphorins are membrane bound or secreted proteins that regulate a number of cellular functions by direct cell-cell contact. Most of their downstream signaling is carried out by the receptors Plexins. Cumulative evidence suggests that Plexin signaling may play a role in neuroimmune disorders. Macrophages and microglia-the resident immune cells of the CNS- form the myeloid lineage and are the first line of defense in CNS injury, contributing to neuroimmunity. Upon injury, we report upregulation of PlexinB2 protein at the lesion site, specifically in cells of the myeloid lineage. Deleting PB2 in CX3CR1+ microglia and macrophages led to impaired motor recovery, increased microglial branch points, and reduced motility; while other physiological functions of microglia, namely proliferation, phagocytosis and lipid metabolism, were unaffected. We report **impaired corralling** - a process in which scar formation for wound healing is hampered - as the cause of hindered motor recovery, and together with microglia RNA-Seq, immunohistochemistry, STED and two-photon imaging, intend to dissect a possible sub-optimal immune-glia crosstalk that may contribute to the phenotype.

(19) IMPROVING LOCOMOTOR FUNCTION AFTER SPINAL CORD INJURY WITH A PERTURBATION-BASED BALANCE TRAINING

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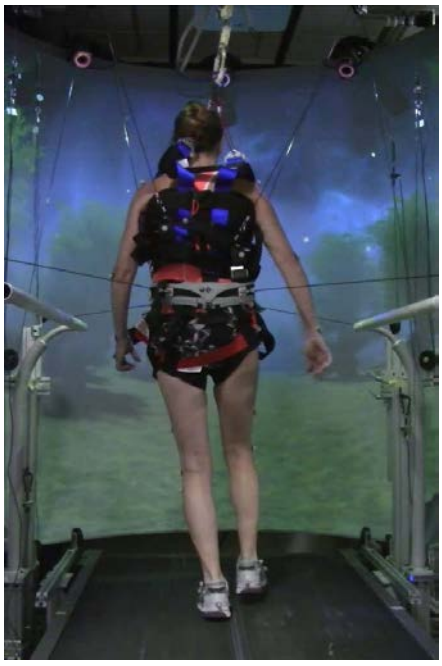

A patient with SCI while reacting to a gait perturbation in the A-TPAD.

The development of new locomotor training interventions is important to modify the recovery process following Spinal Cord Injury (SCI). Our group at Columbia University has developed a novel cable-driven robot, referred to as Active Tethered Pelvic Assist Device (A-TPAD). The A-TPAD can apply controlled force-moments at the human pelvis in all the direction of the space and at precise instants of the gait cycle.

The goal of this project is to develop a new rehabilitative strategy that focuses on improving gait and stability in SCI by providing, at the same time, dynamic body weight support with continuous forces and balance perturbations with unpredictable waist-pulls. This is a unique feature that may be useful to improve balance and reduce the risk of falling in SCI.

Preliminary experiments will be presented to show the capability of the system and feasibility of conducting experiments. After a single training session with the A-TPAD,

where unexpected multi-directional waist-pull perturbations of different intensities were provided, participants modified their balance by adapting both their reactive and proactive strategies. They demonstrated an improved locomotor ability, even when deprived of normal supraspinal inputs.

Supported by SCIRB contract # C32632GG

(20) PHARMACOLOGICAL TARGETING OF ION CHANNELS LEADS TO RAPID AND SUSTAINED BEHAVIORAL IMPROVEMENTS FOLLOWING SPINAL CORD INJURY

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In spinal cord injury, acute cell death is responsible for the primary motor deficit, but it is the slower degeneration of axons that survived the initial insult that prevents future recovery. Current approaches aim to either stop the injury progression or attempt to replace lost cells by transplantation. We however, have hypothesized that restoring function to surviving neurons will be sufficient to cause behavioral improvements and we have approached this idea in two ways. Previous work from our lab has shown that the transplantation of astroglial support cells, which will improve the environment for surviving cells, is sufficient to improve motor function following SCI (PLoS One. 6, e17328). Our recent work with acute spinal cord injury, however, looks to identify a pharmacological agent that would directly act on neurons to improve function and increase survival. To achieve this, we targeted ion channels that are critical for action potential propagation as a way of increasing neuronal activity.

We identified an FDA approved, ion channel-modulating drug that we find leads to rapid behavioral improvements when given 24 hours after thoracic contusion spinal cord injury in Long-Evans rats. The speed of recovery suggests reactivation of the surviving neurons, and remarkably the behavioral improvements are sustained even when the drug is no long administered. Furthermore, we find the drug reduces cell death and consequent lesion volume as early as three days of treatment. Ongoing work investigates further histological changes, as well as pharmacokinetics to understand the mechanism of action and persistent improvements.

Supported by SCIRB contracts #C33280GG-34500 and #C33277GG-3450000

(21) TRAINING UPPER BODY USING A TRUNK SUPPORT TRAINER (TruST)

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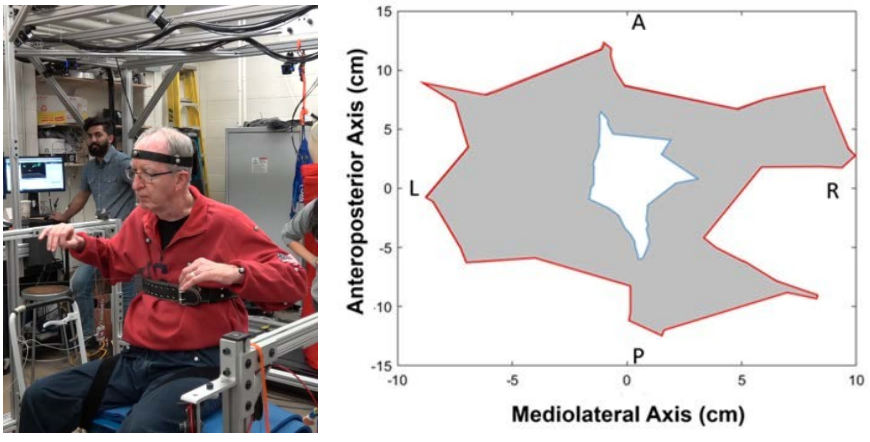

A Trunk Support Trainer (TruST) developed at Columbia ROAR lab for training of upper body posturewith and without force fields

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Adults and children with spinal cord injury (SCI) lose their ability to sit independently due to paralysis of the trunk and limb muscles. Currently, there are no evidenced-based physical rehabilitation interventions to improve seated postural control. Robotics and Rehabilitation (ROAR) lab at Columbia University has developed a novel robotic platform, the Trunk Support Trainer (TruST). It is a motorized cable-driven system that (i) measures the trunk movement in real-time and (ii) applies forces on the upper body safely during tasks that require postural control, both within and beyond the natural workspace of the trunk. Preliminary experiments were conducted in ROAR lab where patients with SCI participated to characterize their trunk range of motion, with and without assistance of TruST. The broad goal of these experiments is to investigate how TruST can be used for characterization and training of seated posture and improve reaching. We believe that TruST can be potentially an effective training tool for patients with SCI who have midthoracic lesions.

(22) A FIBROUS ESTROGEN POLY-PRODRUG SCAFFOLD TO MODULATE ASTROCYTE REACTIVITY

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Following spinal cord injury (SCI), astrocytes undergo detrimental phenotypic changes and prevent tissue regeneration and functional recovery. This change in astrocyte biology is known as astrogliosis. Electrospun fibers are a biomaterial developed to mitigate astrogliosis by providing physical and/or chemical cues that modulate astrocyte phenotype. This project develops a new electrospun fiber scaffold that combines both of these aspects by synthesizing a poly-prodrug formulation of estrogen. This new poly-prodrug, which is directly fabricated into an aligned electrospun fiber guidance conduit, has tunable degradation characteristics allowing for controllable estrogen delivery to a SCI. Multiple studies show that estrogen treatment induces beneficial changes in astrocyte phenotype to better support recovery following SCI.

Thus far, we have synthesized the poly-prodrug estrogen copolymer with a molecular weight of 83.5 kDa (via gel permeation chromatography), and fabricated aligned electrospun fiber guidance conduits directly from the copolymer. We characterized estrogen release from the fibrous scaffolds by submerging a single scaffold in 1 mL of PBS and quantifying estrogen concentration via fluorescence spectroscopy every 24h. Drug release characterization revealed that these scaffolds would degrade over approximately 1.3 years, releasing 0.16±0.03 nmol of estrogen every day. In the coming months, primary rat spinal cord astrocytes will be cultured with these scaffolds. qRT-PCR will be conducted to determine how this new biomaterial affects astrocyte gene expression related to glial scar formation, chondroitin sulfate proteoglycan production, and neurotoxicity; all of which are hallmark characteristics of astrogliosis.

This project represents a departure from traditional biomaterial approaches to treat SCI where a drug is incorporated within a contact guidance scaffold for diffusive release at the injury site. With

our approach, the biomaterial is fabricated directly out of the drug, allowing for controllable, long-term release of a drug with a high regenerative potential following SCI.

Supported by SCIRB contract # C32631GG

(23) WHEELCHAIR ROBOT FOR ACTIVE POSTURAL SUPPORT OF SCI PATIENTS (WRAPS)

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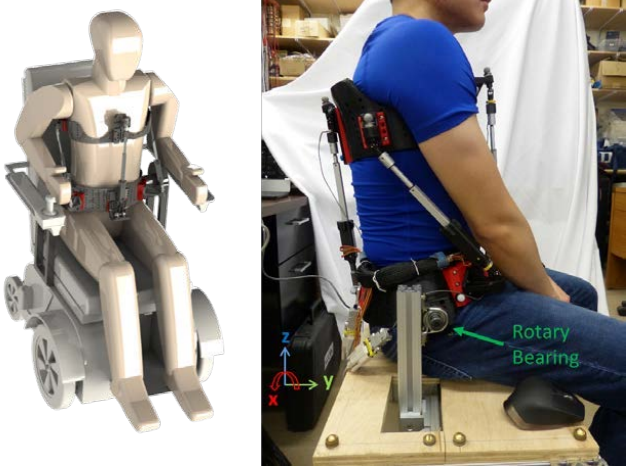

A Wheelchair Robot for Active Postural Support (WRAPS) developed at Columbia ROAR lab for upper body

For most people, sitting up independently and performing everyday tasks such as picking up objects from a shelf, reaching for a cup, using a computer keyboard or a mouse, opening drawers, eating while seated, etc. do not require a second thought. However, for people with limited ability to control the posture while sitting, performing these common daily tasks could be highly demanding, or even impossible. Particularly, it is a challenge for those with a spinal cord lesion in the cervical or high-thoracic regions of the spine.

Recently, the Robotics and Rehabilitation (ROAR) Laboratory at Columbia University has developed a novel Wheelchair Robot for Active Postural Support (WRAPS). This cyber-physical system offers the following features: (i) it can dynamically assist the trunk during reaching movements when sitting in a wheelchair by either controlling the position of the trunk or by applying external forces to it; and (ii) it can be programmed to modify trunk posture of the subject to indirectly affect the Base of Support (BOS). The *objective* of this research is to study how WRAPS can be adapted for wheelchair users with severe SCI.

(24) IDENTIFYING GENES AT THE CORE OF SUCCESSFUL RECOVERY FROM SCI USING *XENOPUS* FROGS

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The frog, *Xenopus laevis*, occupies a transition point in the phylogenetic loss of CNS regenerative capacity. Whereas *Xenopus* successfully recovers from spinal cord injury (SCI) as tadpoles and optic nerve injury (ONI) throughout life, it does not recover from SCI as a frog. We used RNA-seq to identify injury-induced genes shared in common between two regenerative CNS tissues (tadpole SCI hindbrain & frog ONI retina) but not with a non-regenerative tissue (frog SCI

hindbrain). The fraction of the genome exhibiting statistically significant, injury-induced changes in expression ranged from 1.4% (3 day ONI retina) to 11.7% (3 day SCI frog hindbrain), with the vast majority of injury-induced changes being unique to each tissue (>90%). Despite these differences, the numbers of injury-responding genes were similar over time between the regenerative tissues (peaking during maximum regenerative axon outgrowth) and markedly different in the non-regenerative one (peaking soon after injury). At the early post-trauma phase (3 days), injury-induced genes uniquely shared between the two regenerative tissues were primarily pro-inflammatory genes (10), whereas at the late recovery phase (3 weeks), they mainly comprised genes that dampen inflammation and promote wound healing (9). At the peak regenerative phase, 63 additional genes shared between regenerative but not non-regenerative tissues included a mix of pro-inflammatory genes and genes associated with promoting wound healing as well as the transition between the two states. Additional genes shared between regenerative tissues at this phase included ones related to axonal outgrowth (17), DNA replication & repair (16), transcriptional (11) and post-transcriptional control of gene expression (21), cell signaling (36), axon outgrowth (17), the cytoskeleton (31), intracellular transport (22), lipid (14) & general (10) metabolism, and epigenetic changes to chromatin structure (21 genes). Thus, *Xenopus* offers a paradigm for identifying pro-regenerative genes involved in core processes underlying successful CNS axon regeneration.

Supported by SCIRB Contracts C32091, C32249, & C30837 (BGS) and NIH 1R15HD076643-01A1 (KMG)

(25) CHRONIC ELECTRICAL STIMULATION OF THE CST SYSTEM LEADS TO REPAIR AND FUNCTIONAL RECOVERY AFTER SCI INJURY VIA REACTIVATION OF DEVELOPMENTALLY REGULATED MOLECULAR PATHWAYS.

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Cervical injuries are the most common form of SCI. The corticospinal tract (CST) is necessary for controlling voluntary movement and is difficult to repair. We used a neuromodulatory approach to promote skilled movement recovery and repair of the CST after a moderately severe C4 midline contusion in adult rats. We used bilateral epidural intermittent theta burst (iTBS) electrical stimulation of motor cortex (MCX) to promote CST axonal sprouting combined with cathodal trans-spinal direct current stimulation (tsDCS) to enhance spinal cord activation to MCX stimulation after injury. Combined iTBS-tsDCS was delivered for 30 minutes daily for 10 days. tsDCS significantly enhanced motor cortex evoked responses after C4 injury and the combined spinal-M1 neuromodulatory approach promoted significant recovery of skilled locomotion and forepaw manipulation skills. Importantly, stimulation enhanced injury-dependent CST axonal outgrowth below and above the level of the injury.

In the second part of our study, we examined the molecular mechanisms of stimulation-dependent CST axonal sprouting and synapse formation. We used a 14-pulse MCX stimulation protocol, which was shown to enhance outgrowth of spared CST axons and promote motor recovery

following pyramidal tract lesion in our previously published studies. MCX stimulation rapidly upregulated mTOR and Jak/Stat signaling in the corticospinal system. Chronic stimulation, leading to CST sprouting and increased CST presynaptic sites, further enhanced mTOR and Jak/Stat activity. This also shifted the equilibrium of the mTOR repressor PTEN to the inactive phosphorylated form suggesting a molecular transition to an axon growth state. Selective blockade of each signaling pathway revealed that mTOR activation is necessary for stimulation-dependent axon sprouting and Jak/Stat for formation of CST presynaptic boutons.

Our results show that the stimulation of the CST system is an effective neuromodulatory repair strategy for SCI and it promotes repair by reactivating distinct developmentally-regulated signaling pathways for axonal outgrowth and synapse formation.

Supported by NYS SCIRB (C30606GG-JM), NIH (5R01NS064004) and Craig H. Neilsen Foundation (JHM:261214; NZ:385743)

(26) ALPHA-TUBULIN ACETYLTRANSFERASE IS A NOVEL TARGET MEDIATING NEURITE GROWTH INHIBITORY EFFECTS OF CSPGS AND MAG.

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Damage to the central nervous system (CNS) results in neuronal and axonal degeneration, and subsequent neurological dysfunction. Attempts to repair the CNS in adult tissue are deterred, in part, by an inhibitory barrier comprised of chondroitin sulfate proteoglycans (CSPGs) and myelin-associated glycoprotein (MAG) substrates that can inhibit axonal regeneration. Several studies have shown that promoting α-tubulin acetylation is regulated by two opposing enzymes, HDAC6 (deacetylating) and αTAT1 (acetylating). It was previously shown that injury in neurons leads to an increase in HDAC6 expression, and that inhibition of HDAC6 can promote survival and regeneration of neurons. Here, we show that exposure of primary mouse cortical neurons to soluble CSPG and MAG substrates causes an acute and robust reduction in α-tubulin acetylation and αTAT1 protein levels without changes in HDAC6 levels. Distribution studies in neurites show that CSPG and MAG reduce αTAT1 primarily at the distal region. This effect is Rho-kinase-dependent, as pharmacological inhibition of Rho-kinase prevents αTAT1 reduction in response to the growth inhibitory factors. Moreover, CSPG and MAG do not change αTAT1 mRNA at the transcriptional level. Instead, degradation assay shows that these growth inhibitory substrates significantly increase αTAT1 decay and that Rho-kinase inhibition prevents this effect. Together, these findings define αTAT1 as a novel potential therapeutic target for ameliorating CNS injury characterized by growth inhibitory substrates that are prohibitive to axonal regeneration.

Supported by SCIRB contract # C30602 and # C32098

(27) PAIRED THERAPUETIC STIMULATION OF BRAIN AND SPINAL CORD IN A LARGE ANIMAL MODEL OF CERVICAL CONTUSION TO REHABILITATE UPPER-LIMB NEUROMODULATION

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The corticospinal system (CS) is the principal pathway for hand control. Repairing CS inputs to spinal motor networks is an important strategy toward motor rehabilitation after SCI. An emerging therapeutic neuromodulation approach, developed in our lab with a rat model of SCI, uses stimulation of motor cortex (intermittent Theta Burst Stimulation; iTBS) to promote CS outgrowth, combined with spinal cord (transcutaneous spinal Direct Current Stimulation; tsDCS), to augment motor cortex stimulation efficacy. To bridge the translational gap from rat to human we are testing these minimally-/non-invasive approaches in a large animal (feline) model.

A moderate C4 contusion, informed by a finite element method (FEM) study of strain on a segmented model of the spinal column, was produced in adult cats (3.5 mm spherical probe hit at 750 kDyn force with a 1-15 s dwell controlled with an IH-impactor). The stimulation therapy consisted of iTBS (90% of motor threshold applied with an epidural electrode above the arm representation of M1) paired with tsDCS (informed by whole-body FEM predictions of current density to spinal networks: 4mA delivered with 3x3 cm sponge electrode montage with the cathode dorsal to C2-C6 and the anode on the upper chest) delivered for 30 min/day on 10 consecutive days in the chronic injury phase, i.e., after spontaneous recovery had plateaued.

The results show that neuromodulation of motor evoked potentials (MEP), found to be impaired after SCI, were augmented following the paired therapy and supported improved limb control, as seen in rats. Modeling lesion pathology in conjunction with effective dosing of current density to target the impaired spinal segments is a useful translation tool to inform and scale therapy across species. These encouraging findings suggest paired stimulation can be used broadly to strengthen motor cortex-mediated output to limb muscles after cervical injury and improve arm motor function.

Supported by NYS Spinal Cord Injury Research Board contract C31291GG (JM)

(28) PUM2 SHAPES THE AXONAL TRANSCRIPTOME THROUGH RETENTION OF TARGET MRNAS IN THE CELL BODY

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Localized protein synthesis is fundamental for the development, maintenance, and function of neurons. In particular, nerve injury induces rapid local mRNA translation within the injured axons, and the locally produced proteins are required for regeneration. Transcriptomes in axons and soma are distinct but the mechanisms governing the composition of axonal transcriptomes and their regulation during development or regeneration are only partially understood. We found that the binding motif for the Pumilio proteins Pum1 and Pum2 is underrepresented in transcriptomes of axons. Introduction of Pumilio-binding elements (PBEs) into mRNAs containing a β-actin zipcode prevented their axonal localization and translation. Pum2 is expressed only in the soma of neurons, and Pum2-knockdown caused the appearance and translation of PBE-containing mRNAs in axons, including that of GSK3β. Pum2-deficient neurons exhibited axonal growth and branching defects in vivo, and impaired regeneration in vitro. These results reveal that Pum2 shapes axonal transcriptomes by preventing the transport of PBE-containing mRNAs into axons and they identify mRNA retention in the soma as a mechanism for the temporal control of intra-axonal protein synthesis. Pum2 is therefore part of a cell intrinsic mechanism that regulates the innate ability of injured axons to regenerate by shaping the axonal transcriptome.

Supported by SCIRB contract # C32089GG

(29) NONINVASIVE TRANSSPINAL STIMULATION PRODUCES MUSCLE ACTIVITY REVERSALS IN HEALTHY HUMANS DURING TREADMILL WALKING

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Noninvasive transspinal stimulation during walking is a promising approach to promote recovery of motor function in neurological disorders. However, it is not known how transspinal stimulation over the thoracolumbar region affects the phase-dependent modulation of muscle activity. In 13 healthy subjects, transspinal stimulation over the thoracolumbar region was delivered during walking on a motorized treadmill as a single pulse and/or as a pulse train of 330 Hz randomly across the step cycle that was divided into 16 equal bins. Bin 1 corresponds approximately to heel contact, bin 8 to stance-to-swing transition, bin 9 to swing phase initiation, and bin 16 to swing-to-stance transition. EMG signals from ankle extensor and flexor muscles were band-pass filtered and full-wave rectified. The mean EMG amplitude across all bins and steps was calculated and linear EMG envelopes were assembled at 10 Hz. This was done separately for each muscle, and each step corresponding to before, during, and after transspinal stimulation. We found that the EMG activity was similar for steps before and after stimulation. The EMG activity for steps during stimulation with single pulse or pulse train showed that ankle extensors EMG occurred during swing and that of ankle flexor occurred during stance when stimulation was delivered from late stance until swing-to-stance phases. Principle component analysis showed that without stimulation, the majority of EMG activity for ankle extensor and flexor muscles was within the stance and swing phase, respectively. In contrast, during stimulation the major variation of EMG

activity occurred from late stance to mid swing for ankle extensors and from early to mid-stance for flexor. In conclusion, transspinal stimulation has the ability to produce a reversal of EMG activity during walking.

Supported by The Spinal Cord Injury Research Program of the New York State Department of Health (Contracts C32095GG, C32248GG, and C30836GG) and the Craig H. Neilsen Foundation [Grant No. 339705]

(30) SIGNALING PATHWAYS TO REGENERATIVE REPAIR OF SPINAL CORD INJURY: AN INTEGRATIVE MODEL FOR PHARMACOLOGIC EXPLORATION

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Tissues capable of full functional recovery following traumatic or mechanical injury generally exhibit ample capacity to self-initiate regenerative repair. The injured spinal cord, as much as the rest of the central nervous system, shows little propensity to self-initiate regenerative repair. Recent research reports from multiple laboratories are hinting at genomic and biochemical signaling elements that may underlie the spinal cord's reluctance to regenerate. Wondering whether some fundamental organizational principle(s) underlied the roles of the numerous regeneration-associated genes and signaling mediators, we attempted to map the molecules to known cell signaling pathways. Our preliminary findings suggest that two canonical signaling systems account for the majority of known inhibitory or stimulatory mediators: facilitation of ROCK signaling to inhibit regeneration and facilitation of neurotrophin signaling to promote spinal neuroregeneration. We will highlight our strategies for pharmacologically promoting neurotrophin-like signaling (with or without combinatorial suppression of ROCK signaling) to achieve enhanced survival or newbirth of functional neural units for spinal cord injury repair.

Supported by SCIRB Contract# C32247GG

(31) SPINAL LOCOMOTOR CIRCUIT FUNCTION AFTER COMBINED LOCOMOTOR TRAINING WITH PAIRED TRANSSPINAL AND TRANSCORTICAL STIMULATION

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Restoring and maximizing the functional and neuroplastic properties of spared maladaptive spinal neural circuits is a primary target to improve locomotor performance in individuals with incomplete spinal cord injury (SCI). Activity-based therapies, such as locomotor training, normalize the activity of SCI-induced dysfunctional spinal neural circuits thereby correcting sensorimotor function during locomotion. Recent evidence shows that augmenting activity-based therapy with targeted stimulation neuromodulatory protocols, for instance excitatory paired-associative stimulation (PAS), potentiates the beneficial effects of activity training alone in spinal animals. However, the effectiveness of supplementing locomotor training with non-invasive transspinal-transcortical PAS, which facilitates corticospinal excitability, has not been explored in humans with SCI. Therefore, we delivered paired transspinal and transcortical stimuli at an interstimulus interval where transcranial magnetic stimulation (TMS) was delivered after transspinal stimulation

in two people with motor incomplete SCI (AIS C and D) during Lokomat robotic gait training. With foot switches, paired stimuli were delivered during the stance phase of the step cycle in 30 sessions of locomotor training (1h/day, 5 days/week). For transspinal stimulation, the cathode electrode was placed over T10-L1, and two anode electrodes were placed bilaterally on the abdomen, while for transcortical stimulation a double cone coil was placed over M1. Both stimuli were delivered at threshold intensities evoking cortical or spinal motor responses in the soleus muscle. Soleus H-reflex excitability during Lokomat walking was assessed before and after intervention. Transspinal-transcortical stimulation and locomotor training produced a significant depression of the soleus H-reflex during the stance phase, and promoted soleus H-reflex inhibition during the swing phase of the step cycle. Despite being an ongoing project, current findings clearly indicate that this intervention reestablishes the physiological soleus H-reflex phase-dependent modulation in people with motor incomplete SCI. Therefore, augmenting locomotor training with transspinal-transcortical PAS neuromodulation appears to be an innovative paradigm to facilitate locomotor re-learning in SCI.

Supported by New York State Department of Health (NYSDOH), Spinal Cord Injury Research Program (SCIRP) Contracts C32095GG and C32248GG

(32) SUSTAINED DELIVERY OF IL10 AND SHH TO PROMOTE SPINAL CORD REGENERATION AFTER INJURY

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Spinal cord injury (SCI) can result in paralysis for which treatment options are limited. Damage and cell death from the injury promote pro-inflammatory responses such as immune cell activation and recruitment, further enhancing inflammation. However, SCI also induces beneficial anti-inflammatory responses, complicating the search for effective therapies. Therefore, modulating the microenvironment may provide an avenue to reduce inflammation and promote regeneration in the injured cord.

Poly(lactic-co-glycolic acid) (PLGA)-based biodegradable beads that release factors locally offer a clinically compatible method to manipulate the microenvironment while providing long-term modulation and avoiding the side effects of systemic administration. Our lab previously showed that acute, prolonged sonic hedgehog (SHH) exposure in the spinal cord via locally delivered biodegradable PLGA microbeads increases axon sprouting and sparing, reduces scar formation, and improves functional recovery in mice in two SCI models. Since SHH is a growth factor which assists in SCI regeneration, we also targeted the immediate inflammatory environment to reduce the initial damage caused by infiltrating immune cells. Interleukin-10 (IL10) is an anti-inflammatory cytokine shown to have neuroprotective effects following SCI, reducing pain and promoting functional recovery.

Our current work tests the individual effects of SHH beads and IL10 plasmid DNA (IL10pDNA) beads on the inflammatory environment and functional recovery in Long Evans rats after acute and chronic contusive SCI. In vitro, IL10pDNA beads are taken up by macrophages and alter macrophage phenotype.

Preliminary behavioral test results indicate that IL10pbead administration provides functional recovery in the acute, but not chronic phase of injury, while SHH is beneficial in the chronic, but not acute phase. Interestingly, combinatorial treatments of IL10pDNA beads in the acute phase and SHH in the chronic phase shows an additive effect on behavioral recovery. Studies examining the lesion volume and cellular responses to treatment using stereological analysis are on-going.

Supported by NY SCIRB C30605GG (AJA, ST) and Foundation to Cure Paralysis

(33) UNDERSTANDING MOTOR NEURAL CODING THROUGH DETAILED SIMULATION OF MOTOR CORTEX MICROCIRCUITS

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The function and organization of the brain primary motor cortex (M1) circuits -- crucial for motor control -- has not yet been resolved. Most brain-machine interfaces used by spinal cord injury patients decode their motor information from M1, predominantly from large layer 5 corticospinal cells. We have developed the most realistic and detailed computational model of M1 circuits and corticospinal neurons up to date, based on novel experimental data. The model is being used to decipher the neural code underlying the brain circuits responsible for producing movement, understand motor disorders, and contribute to the advancement of brain-machine interfaces for spinal cord injury patients.

Our detailed M1 model includes over 10,000 neurons distributed across the cortical layers. Corticospinal cell models accurately reproduce the electrophysiology and morphology of real neurons. More than 30 million synaptic connections reproduce cell type- and location connectivity patterns obtained from experimental studies. It also simulates inputs from the main cortical and thalamic brain regions that project to M1.

Results provide a more in-depth understanding of how long-range inputs from surrounding regions and molecular/pharmacological effects modulates M1 corticospinal output. We identified two different pathways that activated corticospinal output: 1) inputs from motor-related regions, such as secondary motor cortex; 2) inputs from sensory-related regions, such as somatosensory cortex, triggering M1 superficial layers. Simulated local field potential (LFP) recordings revealed physiological oscillations and information flow consistent with biological data. Also, modulation of HCN channels in corticospinal neurons served as a switch to regulate output, a potential mechanism to convert motor planning into motor execution.

Our work provides insights into how information is encoded and processed in the primary motor cortex. Our detailed computational model provides a useful tool for researchers in the field to evaluate novel hypothesis, decoding methods for brain-machine interfaces and pharmacological or neurostimulation treatments for motor disorders.

Supported by SCIRB contract # DOH01-C32250GG-3450000

(34) TRANSNEURONAL DOWN-REGULATION OF THE PREMOTOR CHOLINERGIC SYSTEM AFTER CORTICOSPINAL TRACT LOSS

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Injury to the brain and spinal cord, especially the corticospinal tract, leads to movement impairments. In addition to direct disruption of descending motor pathways, spinal motor circuits that are caudal to and not directly damaged by the lesion undergo remodeling that contributes significantly to the impairments. Knowing which spinal circuits are remodeled and the underlying mechanisms are critical for understanding the functional changes in the motor pathways and for developing repair strategies. Here we study spinal premotor cholinergic interneurons that directly modulate motoneuron excitability via their cholinergic C-bouton terminals. Using a model of unilateral medullary corticospinal tract lesion in male rats, we found transneuronal down-regulation of the premotor spinal cholinergic pathway. Phagocytic microglial cells were up-regulated in parallel with cholinergic pathway down-regulation, and both were blocked by minocycline, a microglia activation inhibitor. Additionally, we found a transient increase in interneuronal complement protein C1q expression that preceded interneuron loss. Three-dimensional reconstructions showed ongoing phagocytosis of C1q-expressing cholinergic interneurons by microglia 3 days post-injury, which was complete by 10 days post-injury. Unilateral motor cortex inactivation using the $GABA_A$ receptor agonist muscimol replicated the changes in neuronal C1q expression and phagocytic microglia cells detected at 3 days after the lesion, and also led to neuronal loss, indicating an activity-dependence. The neuronal loss after the lesion was rescued by increasing spinal activity using cathodal trans-spinal direct current stimulation.

Our findings indicate that modulation of cholinergic premotor interneurons after CST injury strongly depends on the activity of the corticospinal pathway. It involves early over-expression of neuronal complement protein C1q and is completed by microglial phagocytosis using C1q as an “eat-me” signal. Our findings provide the mechanistic insight that maintaining activity, possibly during a critical period, helps protect caudal motor circuits from further damage, and as a result, may improve motor functional recovery and rehabilitation.

(35) MOTOR CORTEX AND CERVICAL SPINAL CORD ELECTRICAL STIMULATION PROMOTES FORELIMB MOTOR FUNCTION AFTER SPINAL CORD INJURY IN RATS: A REPLICATION STUDY

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Most cervical spinal cord injuries (SCI) spare some axons at the lesion, including the corticospinal tract (CST), which is critical for voluntary movement. We targeted spared CST connections using paired stimulation of motor cortex and spinal cord. We hypothesized that electrical stimulation would improve forelimb function and promote CST axon sprouting below the injury site. Although many SCI studies are being conducted, there are few reports of successful replication, preventing new treatments from reaching the clinic. This study validates a previous positive study using paired stimulation after SCI from John Martin's laboratory at CUNY, and establishes a standard methodology to follow for SCI study replication.

The stimulation approach combines intermittent theta burst stimulation of forelimb motor cortex with non-invasive trans-spinal direct current stimulation. Before injury, rats were trained on skilled ladder walking and food manipulation (IBB) tasks. Then all animals received C4 contusion SCI (200kdynes) and randomized into stimulation and control groups. The stimulated rats received paired stimulation daily from day 11-20 post injury. Controls received sham stimulation. All rats were assessed on the same behavior tasks weekly from weeks 4-7 after injury. CST axons in the spinal cord bilaterally above and below the lesion site were traced with BDA and quantified. All assessments were performed by experimenters blinded to the treatment allocation.

Stimulation animals achieved significantly better forelimb motor function recovery, evidenced by fewer stepping errors on the skilled walking (stimulation: 33.90%±9.32%, control: 50.68%±18.16%, p=0.013) and higher scores on the IBB task(stimulation: 7.20±0.84, control: 5.23±2.56, p=0.025). Stimulation animals also had significantly higher CST axon density in the spinal cord below the lesion on the ipsilateral side of stimulation, but not on the contralateral side. The large effect size and the replication in independent laboratory validates this approach, which will be trialed in cats before being tested in people.

Supported by NYS contract# C31291GG

(36) PROGRESSIVE SUBLESIONAL BONE LOSS OCCURS INTO THE SECOND DECADE AFTER SCI

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Objective: The rate of areal bone mineral density (aBMD) loss at the knee [distal femur (DF) and proximal tibia (PT)] and hip [femoral neck (FN) and total hip (TH)] was determined in persons with

traumatic spinal cord injury (SCI) who were stratified into subgroups based on time since injury (TSI).

Research Methods: A cross-sectional retrospective review was performed to compile knee and hip aBMD values obtained by dual energy x-ray absorptiometry (GE Lunar iDXA) on 105 individuals with SCI (TSI ≤ 12 months, n=19; TSI 1-5 years, n=35; 6-10 years, n=20; TSI 11-20 years, n=16; TSI >20 years, n=15) and 17 able-bodied reference (AB_{ref}) controls. Standard clinical software for the proximal femur was employed in conjunction with proprietary research orthopedic knee software applications. Young-normal (T-score) and age-matched (Z-scores) standardized scores for the FN and TH were obtained using the combined GE Lunar/National Health and Nutrition Examination Survey (NHANES III) combined reference database.

Results: When the subgroups with SCI were compared as epochs of TSI, significantly lower mean aBMD and reference scores were observed as TSI increased. Loss in aBMD occurred at the DF, PT, FN, and TH with the variance in loss being 46%, 49%, 32%, and 43%, respectively, which is described by the exponential decay curves with a time to steady state after SCI occurring at 14.6, 11.3, 14, and 6.2 years, respectively. Compared to the ABref group, aBMD at steady state was 30-50% lower at the hip and knee in the SCI group.

Conclusions: Because steady state bone loss is not reached until many years longer than expected after acute SCI, clinicians and therapists may have a larger window of time than was previously assumed to prescribe pharmacological and/or mechanical interventions to prevent the insidious progression of sublesional skeletal deterioration.

Acknowledgements: The authors wish to thank the New York State Department of Health Spinal Cord Injury Research Board [DOH01-PART3-2019-00002]

(37) EFFECTS OF SPINAL ELECTRO-MAGNETIC STIMULATION ON NEUROPHYSICIOLOGICAL RESPONSES IN PEOPLE WITH SCI COMPARED TO HEALTHY CONTROLS

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Non-invasive spinal electro-magnetic stimulation (SEMS) was applied over the spinal cord for participants with and without spinal cord injury (SCI) to determine the neurophysiological responses in the spino-neuromuscular circuits. Our hypothesis was that H-reflex responses evoked by tibial nerve stimulation (TNS) would be different within and between groups after SEMS administration. Soleus muscle H-reflex recruitment curves were measured pre-post SEMS using TNS. Each H-reflex curve was normalized with its H-max, then fitted with a fractional polynomial function for further analysis. In SCI, a significant leftward shift of the H-reflex responses after 30 minutes of SEMS was observed, indicating a decreased threshold current intensity compared to pre-SEMS. Within- and between-group comparisons of pre-post changes were tested using nonparametric Wilcoxon tests. There was a significant leftward H-reflex curve shift at 50% and 100% of its H-maximum for SCI (n=3, 14 trials-pre-SEMS and post-SEMS), 50% pre-SEMS

Mean±SD 1.14±0.10; 50% post-SEMS 0.96±0.17, p-value=0.0052 and for 100% pre-SEMS Mean±SD 1.67±0.37, 100% post –SEMS 1.43±0.31, p-value=0.0001). The healthy group (n=4, 18 trials-pre-SEMS and post-SEMS) also showed a significant leftward shift (50% pre-SEMS, Mean±SD 1.19±0.07, 50% post-SEMS 1.02±0.24, p-value=0.0090 and for 100% pre-SEMS Mean±SD 1.54±0.15, 100% post-SEMS 1.38±0.34, p-value=0.0304). There was no significant difference of this shift between groups however a trend toward a reduced curve shift in SCI compared the healthy pre-vs.-post SEMS existed. These results indicate that the SCI group did not adapt similarly to SEMS with the same lower threshold of TNS as the healthy group. Despite the trend of lower changes in this TNS stimulation threshold in SCI, the lack of significant group differences could be due to variability in injury level and injury asymmetry. Our results indicate that SEMS, as a non-invasive treatment that could be applied clinically, facilitates sensorimotor function (reinforced by AIS exams) and thus functional performance of SCI individuals.

Supported by SCIRB Contract C32097GG

(38) INHIBITION OF NICOTINIC ACETYLCHOLINE SIGNALING IMPAIRS MOTOR LEARNING

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Basal forebrain cholinergic neurons are known to play an essential role in motor learning. However, the underlying molecular and circuit mechanisms remain elusive. Here, we show that blockade of nicotinic receptors by systemic injection of mecamylamine (MEC) and methyllycaconitine (MLA) significantly attenuated skilled motor learning on the recessed single pellet retrieval task. MEC and MLA-treated mice showed smaller improvements over the course of training. MEC and MLA treatment did not affect baseline performance during the initial phase (training days 1-3), but the mean values during the rising (days 6-8) and plateau (days 11-14) phases were significantly lower in drug-injected animals than that in controls. Wash out of MEC and MLA enabled the mice to learn the task. Thus, our preliminary findings demonstrate a crucial role for nicotinic receptors in the acquisition of motor learning. We will employ transgenic models to identify the location and corresponding receptor subunits that contribute to motor learning. The potential contribution of motor learning mechanisms in rehabilitation after spinal cord injury is also being investigated.

Supported by SCIRB contract # DOH01-FLLOW2-2016-00006

(39) DEVELOPING VAGUS NERVE STIMULATION FOR MODIFYING URINARY FUNCTION IN UNANESTHETIZED, FREELY-MOVING RATS

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Spinal cord injury (SCI) interrupts the brain's control of external urethral sphincter (EUS) and bladder activity, frequently resulting in abnormal lower urinary tract (LUT) function. Current treatments provide symptomatic relief, but do not address the underlying causes. Vagus nerve stimulation (VNS), when paired with specific behaviors, induces focused and durable plasticity that induces beneficial plasticity in animal models of nervous system disorders. We hypothesize that VNS paired with the appropriate phase of voiding will induce neuronal plasticity that affects

LUT function. This study seeks to develop methods for applying VNS during cystometry to assess VNS effects on LUT function in freely-moving spinal-intact rats.

Female rats are implanted with a suprapubic bladder catheter, EUS electrodes, and a left cervical VNS cuff; wires and catheter were exteriorized to skull-mounted connectors for infusing saline and measuring bladder pressure, recording EUS EMG, and VNS, respectively. After ≥1-wk recovery, rats are placed in a metabolic cage, where urine is collected and weighed continuously during voiding induced by saline infusion into the bladder. Voiding data are recorded sequentially: with no stimulation; with VNS paired with either bladder pressure peak during voiding or the EUS bursting activity that precedes peak pressure; and again with no stimulation.

Initial results from two rats show that VNS applied during peak bladder pressure increased void size and EUS bursting duration, while VNS paired with EUS bursting decreased void size and reduced EUS bursting duration. These effects persisted for at least 30 min after the end of stimulation. The results suggest that: VNS can affect LUT function in spinal-intact rats; the precise timing of the VNS determines the nature of the effect; and the effects can outlast the period of stimulation. If further studies confirm these early data, targeted VNS could offer a novel approach to treating disorders of LUT function.

Supported by SCIRB contract # C32241GG and NIH/NIBIB 1P41EB018783

(40) PROMOTING AXON GROWTH AND SYNAPTOGENESIS AFTER SPINAL CORD INJURY

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The main focus of the Zhong laboratory is on the mechanisms of axon growth. Axons grow robustly during fetal development, but mature axons dramatically lose the ability to grow. In case of injury or degeneration, axons are able to regenerate to some degree in the PNS, but not at all in the CNS. We (and many others) hypothesize that re-activation of the fetal cell-intrinsic growth pathways may increase growth competency in adult CNS neurons and enable axon regeneration in the CNS after injury.

Using genetically modified mice we have demonstrated that activation of the RAF-MAP kinase signaling pathway in adult retinal ganglion neurons promotes axon regeneration in the optic nerve after crush injury. New data indicate that the same intervention also enables substantial regenerative growth as well as collateral sprouting of corticospinal tract (CST) axons in several mouse models of spinal cord injury. We currently focus on demonstrating de novo synaptogenesis involving regenerating or sprouting CST axons. For this purpose, we are developing genetically encoded anterograde transsynaptic tracers to label the regenerating axons and their downstream post-synaptic target cells. Emerging synaptic connectivity will be monitored using a custom-built 3-photon excitatory fluorescence microscopy system. We also plan to take advantage of transsynaptic tracing combined with in vivo Ca2+ imaging to gain new insight into the plasticity of pain circuitry in spinal cord injury models, as intractable neuropathic pain is a major complication associated with traumatic injuries to the nervous system.

Finally, we collaborate with clinical researchers to explore noninvasive techniques of activating intracellular growth signaling cascades in the CNS, in hopes of triggering useful axon regeneration

or sprouting in spinal cord injury patients. elucidating the mechanisms required for spinal cord regeneration.

Supported by SCIRB contract C33270GG and C32092GG

(41) IDENTIFYING POTENTIAL NEURAL CANDIDATES INVOLVED DURING CERVICAL EPIDURAL STIMULATION IN RODENTS

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Regaining upper-limb function remains the top priority of population suffering from cervical spinal cord injury (cSCI). Recent studies have shown that electrical epidural stimulation (ES) of the cervical cord facilitates upper-limb functional recovery post-SCI. One of the proposed mechanisms for motor recovery following ES is the facilitation of sensorimotor neural networks. However, the spinal networks activated by cervical ES remain largely unknown. Determining which pathways are modulated is a critical next step to pinpoint components involved in recovery and will aid in the design of targeted therapies.

In this work, we seek to determine the electrophysiological mechanisms underlying cervical ES. We begin by identifying spinal structures that are activated with cervical ES using in-vivo spinal motor evoked potentials (SMEP). Two protocols were implemented for this purpose: A) Single pulse stimulation B) Paired-pulsed stimulation of the C6 and/or C8 spinal segments. We generated ~500 evoked responses per rat at 8 different intensities (100-800μA) and recorded SMEPs from forelimb muscles via chronically implanted EMG electrodes from 12 non-injured rats. Our data show that the SMEPs generally comprise of three distinct waveforms based on the latency, amplitude, and spike morphology. We identify these waveforms as early (ER), middle (MR) and late (LR) responses. Similar to findings in the lower limb, the ER amplitude appears at higher stimulation intensities and plateaus in amplitude at the highest stimulation intensities; indicative of direct activation of efferents. The MR in contrast, appears only at lower stimulation intensities; indicative of lower threshold afferent circuitry. Preliminary paired-pulse data also show that the MR from the first pulse in a paired-pulse protocol is consistently modulated (abolished or amplified) at specific inter-stimulus intervals and amplitudes; supporting the idea that the MR has monosynaptic properties, influenced by presynaptic inhibitory and/or excitatory interneurons. The LR contains prolonged, unsynchronized spiking activity; indicating polysynaptic origin.

(42) PERICYTE ATTENUATION COMBINED WITH ADENOVIRAL ACTIVATION OF B-RAF AND C-RAF MAY IMPROVE AXON REGENERATION AFTER SPINAL CORD INJURY

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In the fetus, neurotrophic factors trigger the Ras-Raf-MEK pathway to stimulate long axon growth. However, this pathway is downregulated in adult neurons. Reactivating it may be the key to inducing axon regeneration and functional recovery after spinal cord injury. Indeed, constitutive activation of the B-Raf kinase (via V600E mutation) in a conditional knock-in mouse model induces substantial axon regenerative growth in the spinal cord after a crush injury (O'Donovan et al., 2014).

The growing axons, however, frequently have trouble crossing fibrotic scar tissue

induced by pericyte proliferation. Here we aim to study the effect of activated B-Raf and C-Raf in a mouse model of attenuated pericyte proliferation. We hypothesize that reduction of fibrotic scar tissue by pericyte attenuation will improve upon the axon regeneration that we have seen with Raf activation alone. To test this hypothesis, we have generated adeno-associated viruses (AAVs) encoding B-Raf and C-Raf modified with a C terminal CAAX motif, which drives Raf recruitment to the plasma membrane. Injection of these viruses into the motor cortex of wild type mice increases the activating phosphorylation of the Raf effectors MEK and ERK. Furthermore, viral injection prior to dorsal root crush of the C5, C6, C7, and C8 dorsal roots results in significant axon extension past the crush site. We are now injecting the viruses into motor cortex of mice with attenuated pericyte proliferation, expecting that the combination of reduced fibrotic tissue and activated Raf will result in increased axon growth and functional recovery as measured by the horizontal ladder-walking test. Moreover, we hypothesize that combining these treatments with targeted deletion of the phosphatases PTEN and DUSP6 by shRNA will result in further growth and recovery. As AAVs are FDA approved treatments that can be used in spinal cord injury patients, this work will ultimately advance the field of spinal cord injury by revealing novel mechanisms that can enable spinal cord axon regeneration.

Supported by SCIRB postdoctoral fellowship C33611GG

(43) POTENTIAL BENEFITS OF SINGLE BOUT ACUTE INTERMITTENT HYPOXIA (AIH) COMPOSED OF 10% OR 12% O_2 ON LOWER URINARY TRACT (LUT) FUNCTION 4-WEEKS AFTER MODERATE CONTUSION MID-THORACIC SPINAL CORD INJURY (SCI)

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AIH has been reported to induce spinal motor plasticity in rodents and humans with incomplete SCI, and as such has been proposed as a potential therapeutic intervention for treatment of chronic motor incomplete SCI. We have begun to characterize potential beneficial effects of AIH to improve LUT function following mid-thoracic contusion SCI, with the goal of the current study focused on identifying an effective level of hypoxia in the AIH protocol sufficient to elicit functional improvements in LUT behaviors with minimal detrimental hypoxic effects. To accomplish this, we examined the effects of single bout AIH consisting of three 5-min episodes of either 10% or 12% O_2 on bladder intravesical pressure and urine output during continuous infusion of saline (0.04-0.07 ml/min) into the bladder in urethane-anesthetized, spontaneously breathing adult female Sprague-Dawley rats 4-weeks after mid-thoracic contusion (200 kilodynes) SCI. Before AIH, bladder behavior was characterized by pronounced rhythmic bladder activity consisting of a series of non-voiding bladder contractions with increasing amplitude that preceded a voiding bladder contraction. Exposure to hypoxia (AIH) increased the frequency of rhythmic bladder contractions and output volume. Following the end of AIH, there was a delay to the next voiding bladder contraction followed by a more normal pattern of bladder activity (compared to baseline), which was characterized by fewer non-voiding bladder contractions, increased output volume per void, and emergence of threshold-driven bladder contractions that persisted for up to 120 minutes post-AIH. While both levels of hypoxia produced post-AIH improvements in bladder function, the differences observed appeared to be restricted to hypoxic and immediate post-hypoxic exposures with only minimal differences in post-AIH-induced effects. While these data indicate that exposure

to single bout AIH using either 10% or 12% O_2 results in improved LUT-related behaviors in SCI rats, the more mild 12% O_2 hypoxic stimulus may be better tolerated.

Supported by NYS DOH SCIRB Contract # 32088GG

(44) VISUALIZING THE ACTIVITY OF CORTICOSPINAL MOTOR NEURONS *IN VIVO*

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Corticospinal motor neurons (CSMNs) control motor function. Monitoring the changes in CSMNs activity after spinal cord injury is one way to assess ongoing recovery. However, there is no established non-invasive and non-toxic protocol to assess the activities of CSMNs over time. In this study, we are using a *fezf2-CreER^{T2}* mouse line to selectively and inducibly target reporter gene expression in layer V/VI motor cortex. Using two-photon excitation fluorescent imaging system, we have first assessed the efficacy of enhanced green fluorescent protein (eGFP) and tdTomato (tdTom) imaging in the *fezf2-CreER^{T2}* targeted cells in adult mice. Our preliminary results indicate that tdTom, but not eGFP, is suitable for *in vivo* imaging at 600-700 um deep in motor cortex in awake mice. To detect spontaneous Ca^{2+} transients, we have generated mice harboring *fezf2-CreER^{T2} : LSL-kaBraf : LSL-eGFP : LSL-rtTA3 : TRE-LSL-RCaMP1.07* alleles. Tamoxifen/Doxycycline-inducible *RCaMP1.07/eGFP* expression has been confirmed in CSMNs. We are currently setting up a three-photon excitation fluorescent imaging protocol for live imaging of the Ca^{2+} transients in CSMNs, first in intact animals. Analysis will then proceed to mice subjected to spinal cord injury surgeries, either unilateral pyramidotomy or dorsal hemisection, to determine changes in CSMNs activities associated with CNS axon sprouting or regeneration *in vivo*. This study will provide a crucial tool for investigating the association between CSMNs activities and motor behaviors.

Supported by SCIRB postdoctoral fellowship C30863GG

(45) EFFECTS OF SINGLE BOUT MODERATE ACUTE INTERMITTENT HYPOXIA (AIH) ON LOWER URINARY TRACT (LUT) FUNCTION 1-WEEK FOLLOWING MID-THORACIC CONTUSION SPINAL CORD INJURY (SCI)

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Ongoing studies in our laboratory demonstrate improved LUT function following exposure to moderate AIH in rats 4-weeks post-SCI. This time point corresponds to a time when the initial recovery from SCI has stabilized and rats are able to spontaneously void. The goal of the present study was to assess the therapeutic potential of single bout AIH presented at 1-week post-SCI when rats exhibit more severe LUT dysfunction and are just beginning to show signs of initial recovery. To accomplish this, we recorded bladder intravesical pressure, external urethral sphincter (EUS) EMG activity, and urine output during continuous infusion of saline (0.04-0.07 ml/min) into the bladder before, during, and after single bout AIH consisting of three 5-min episodes of 10-12% O_2 in urethane-anesthetized, spontaneously breathing adult female Sprague-Dawley rats 1-week after mid-thoracic contusion (200 kilodynes) SCI. In the majority of rats,

bladder activity was dominated by rhythmic small amplitude non-voiding bladder contractions that continued during bladder filling, and in every case, bladder pressure and power of high frequency (HF) EUS spectral activity gradually increased until the onset of leakage. Subsequent exposure to hypoxia (AIH) produced larger volume voids associated with transient decreases in bladder pressure without obvious bladder contractions and a marked reduction in EUS HF spectral power albeit some high powered HF spectral activity was seen between hypoxic bouts. Post-AIH, an extended period of elevated bladder pressure characterized by small amplitude pressure fluctuations with continuous leakage occurred although in a subset of rats (~15%), bladder behavior was converted to activity that included voiding bladder contractions. In both groups of SCI rats, a more regular pattern of EUS HF spectral activity that included phasic high-power episodes emerged post-AIH. These data suggest that exposure to moderate AIH during the early post-SCI period elicits voiding and reorganizes network components underlying EUS spectral activity.

Supported by NYS DOH SCIRB Contract # 32088GG

(46) REPEATED X-RAY MICROBEAM IRRADIATION OF THE RAT SPINAL CORD CONTUSION INJURY PRODUCES SUBSTANTIAL HIND-LEG FUNCTIONAL RECOVERY

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Spinal cord injury (SCI), specifically contusion injury, is a major health problem with no current effective treatment. Studies with rats have shown that irradiation of contusion injury with conventional x-rays in the first few days post-injury improves their hind-leg function. However, such irradiations at the doses used can produce late radiation effects if used clinically. This long-term radiation damage can be mitigated by using a collimator to segment the solid beam into arrays of thin (~0.3 mm), parallel planes of x rays, called x-ray microbeams. The tissue-sparing effect of microbeams (≤0.3 mm) and their counterpart, minibeams (>0.3 mm, <0.7 mm), has been demonstrated by experiments with synchrotron x rays and recently by orthovoltage x rays. Results are presented from inducing spinal cord contusion injury in rats by a 25 mm rod drop at T9 and T10 using the NYU impactor and subsequently irradiating the rat SCI with 100 kVp microbeams at three dose fractions in the first 12 days after the injury. To determine the effects of the radiation on the contusion injury, the rats were scored using the BBB scoring method, which utilizes a 0-21 scale, with 0 being complete paralysis and 21 being full mobility. Seven months post-injury, all of the irradiated rats presented BBB scores of 14-18, while the average score of the non-irradiated controls was 10.5. This functional improvement has been tentatively attributed to the ablation of astrocytes and infiltrating immune cells, including macrophages, which are peaked in their population at the times of the irradiations. These results suggest that minibeam irradiation could become a new treatment method of SCI, using either high-power orthovoltage x-ray machines or compact synchrotrons. Future research will involve producing a larger sample size to gain adequate significant data to propel the research towards early stage human clinical trials.

(47) SELECTIVE MAPK PATHWAY ACTIVATION IN ADULT CST NEURONS AS A STRATEGY FOR CNS SPROUTING AND REGENERATION AFTER SPINAL CORD INJURY

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Central nervous system (CNS) injuries usually result in permanent loss of connectivity between the injured axons and their postsynaptic targets. Promoting axon regeneration and synaptogenesis after CNS injury is a great challenge due to the non-permissive environment at the lesion site and reduced intrinsic ability of adult axons to regenerate. Furthermore, synaptogenesis in the injured spinal cord has not yet been directly observed, and the mechanism by which newly formed axons make and maintain new synaptic connections to replace lost ones remains largely unknown.

We used a genetic approach to show that activation of the RAF – MEK signaling cascade, a key neuro-intrinsic signaling cascade regulating embryonic axon growth, is not only necessary but also sufficient to promote corticospinal motor neuron axon regrowth after experimental spinal cord injury (SCI). We documented strong regenerative axon growth caudal to the injury sites after T8 dorsal hemisection or complete crush and contralateral sprouting after unilateral pyramidotomy. Axon regeneration in experimental mice correlated with improved sensori-motor function recovery as assessed with open field and horizontal ladder test. Furthermore, we developed a powerful tool that can be used to evaluate the synaptogenesis of regenerating and sprouting axons. We show that injection of a transsynaptic tracer in the motor cortex of mice subjected to unilateral pyramidotomy can be used to label the CST postsynaptic targets, propriospinal interneurons.

These data suggest that re-activation of the cell-intrinsic RAF – MEK pathway can greatly elevate the growth competency of adult CNS neurons and promote synaptogenesis of the injured CST opening new therapeutic perspectives for treating SCI.

(48) *IN VIVO* THREE-PHOTON EXCITED FLUORESCENCE IMAGING IN THE SPINAL CORD OF AWAKE, LOCOMOTING MICE

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Spinal cord injury (SCI) is a devastating neurological disorder afflicting more than 2.5 million people worldwide. SCI severs axonal tracts, leading to decrease in supra-spinal input to the neurons caudal to the lesion site. Central pattern generators (CPGs) are defined interneuron networks located about halfway into the spinal cord that relay a mixture of excitatory and inhibitory signals and drive ventral motor neurons to coordinate rhythmic locomotor behavior. However, these cells sit below the highly optically scattering white matter, making imaging of these cells challenging, even with two-photon microscopy. Recent work has shown that utilizing higher order

nonlinear optical processes, such as three-photon excited fluorescence (3PEF), enables deeper penetration into scattering tissue. Here, we explore the use of 3PEF imaging using a 1.3-µm excitation source to image cellular structure and function in the mouse spinal cord. We first imaged the topology of the microvascular network and measured blood flow speed throughout the vascular hierarchy, from the lateral arterioles, through the capillary bed, and to the dorsal spinal vein. Next, we examined the response of microglia (GFP) and dorsal ascending axons (YFP) to occlusion in the venules (QDot 655) that drain the spinal cord. The surgical preparation we use to gain optical access to the spinal cord enables us to spine fix the mice, while awake, under the microscope. Mice can then "run" on a spinning disk while we image their spinal cord. Once trained, mice exhibited a normal running gait and grooming behaviors while spine fixed atop the disk. We then used 3EPF imaging of the genetically-encoded calcium sensor GCaMP6s to measure neural activity in spinal cord neurons. In mice expressing GCaMP in sensory neurons (CaMKIItTA-GCaMP6s), we observed stimulus-locked neural responses (dF/F > 50%) in response to electric shocks to the hind paw. When these animals were awake under the microscope, the neural firing frequency, as well as the amplitude of the calcium response, increased as the mouse went from a resting state to continuously running on the disk. In efforts to image activity in some of the CPG neurons that control limb motion, we delivered AAV9-LoxP-GCaMP6s virus into the spinal cord of Chx10-Cre animals. This led to GCaMP6s expression in V2a cells, which reside ~500 µm underneath the cord surface. When combined with quantitative tracking of limb kinematics, this capability for 3PEF imaging of cell-resolved neural activity could enable detailed studies of how activity patterns in CPG circuits coordinate rhythmic locomotion and how their firing changes after SCI.

(49) CORTICOSPINAL NEURON ACTIVITY DURING SKILLED MOTOR LEARNING AND AFTER INJURY

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Current behavioral tools in mice are not sufficient for interrogating complex, corticospinal-dependent, skilled motor behavior. The foundation for skilled motor learning and a potential mechanism for rehabilitation after spinal cord injury is the remodeling of cortical motor networks, including corticospinal neurons. An understanding of the organization and function of cortical motor networks is critical as neurological diseases and injuries that disrupt these networks, or network output, dramatically impair motor function. Recent advances in optical imaging have allowed for the interrogation of cortical motor network function *in vivo.* In mice, a simple lever press task has provided the initial insights into network function during learning, however, the execution of this unskilled learned behavior is unaffected by motor cortex injury. We have addressed this critical need by developing unbiased testing devices for complex behaviors to use in concert with modern *in vivo* imaging techniques.

We have adapted automated behavioral tasks for use in head-fixed mice during two-photon imaging. We have validated two skilled motor tasks, critical for dexterity in mice: 1) Isometric pull task and 2) supination task, which is the ability to turn the paw from palm down to palm up. We tested the impairment of behavioral performance induced by unilateral transection of the corticospinal tract at the medullary pyramids (pyramidotomy). We recorded calcium transients in individual corticospinal neurons expressing the genetically encoded calcium indicator GCaMP6f.

Imaging was performed over the course of skilled motor learning and used to determine the effects of pyramidotomy on neuronal activity. Our findings on the corticospinal neuron response to injury will open the door to future studies that focus on the plasticity of cortical motor networks, the incorporation of individual corticospinal neurons during skilled motor learning, and the recovery of motor networks after spinal cord injury.

Supported by the NIH Common Fund 1DP2NS106663, NINDS R03NS103070

(50) MODULATION OF NEURONAL CYTOSKELETON TO REPAIR SPINAL CORD INJURY AND TREAT UROGENITAL DYSFUNCTION

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Approximately 12,000 new cases of spinal cord injury (SCI) occur every year in the United States. SCI results not only in the loss of patient mobility, but also impaired bladder, bowel and sexual/erectile function. Indeed, recovery of urogenital functions are listed by SCI patients as a top priority.

The major impediment to recovery of function after SCI is the inability of damaged neurons within the CNS to regrow their axons and overcome inhibitory cues and obstacles to reinnervate appropriate targets. We recently identified a novel microtubule severing enzyme, termed Fidgetin-like 2 (FL2), which exerts profound inhibition of axonal growth.

Using a rat compression model of SCI, we investigated the ability of FL2 depletion at the site of injury (achieved via application of nanoparticle encapsulated FL2 siRNA; FL2 siRNA-np) to improve motor, bladder and erectile function. Animals treated with FL2 siRNA-np demonstrated significantly improved motor function at Day 4 after SCI when compared to control SCI rats treated with scramble siRNA containing nanoparticles. FL2 siRNA-np treated SCI rats also had improved bladder function as evidence by lower urine expressed volumes as early as 4 days after SCI, and by cystometric findings of increased voided volume and bladder compliance, and decreased micturition frequency, threshold pressure, micturition pressure and spontaneous activity at 2 weeks after SCI. Moreover, SCI rats treated with FL2 siRNA-np had a trend towards improved erectile response as determined by electrostimulation of the cavernous nerve resulting in an increased intracavernous pressure (ICP) when compared to control animals.

Overall, our results demonstrate that strategies devised to knock-down FL2 at the time of SCI have the potential to improve motor, bladder and erectile function outcomes.

(51) CLOSED-LOOP LEARNING CONTROL FOR AUTOMATIC FES-INDUCED CYCLING

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Functional Electrical Stimulation (FES) technologies seek to enhance the quality of life of people with movement disorders. The use of robotic devices and the artificial activation of muscles via FES aim to restore mobility in paralyzed limbs and promote active movements for people with neurological conditions. Closed-loop control of FES coupled with motorized assistance in cycling is an effective exercise to activate lower-limb muscles and exploit the physiological benefits of electrical stimulation. In addition, the exercise duration can be prolonged due to the assistance provided by an electric motor mounted to a stationary cycle. However, a fundamental question during the implementation of hybrid technologies (i.e., combined FES and motorized assistance) for spinal cord injury (SCI) rehabilitation is how the control should be shared between the machine (i.e., the motorized cycle) and the human (i.e., FES delivered to the muscles) to yield subject-specific, safe, and adaptive rehabilitation.

This project focuses on the development of switched learning controllers that activate lower-limb muscles based on kinematic efficiency and engage the motorized assistance only when most needed. Experimental results of closed-loop FES-induced cycling for cadence (speed) and power tracking in three SCI subjects are presented to demonstrate the feasibility of the control methodology. Consistent repeatable cycling was obtained despite the differences in motor skills of the participants, uncertainty in the closed-loop system, and other challenges related to the application of surface neuromuscular electrical stimulation. The preliminary results show a promising path for longitudinal studies and to further improve the robustness of the closed-loop control methodology. This project seeks to advance the research in the field of SCI rehabilitation, particularly, toward function restoration by levering novel advances in switched control methods. The developed research has far-reaching implications in therapies involving exoskeletons and body weight support treadmill training during bipedal locomotion.

(52) A DEVICE-ASSISTED SURGICAL PROCEDURE TO PROVIDE A CONTROLLED BIOPHYSICAL ENVIRONMENT FOR SPINAL CORD REGENERATION

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Objective: to develop a surgical procedure centered on an implantable degradable device able to provide a suitable biophysical environment to protect and guide spinal cord regeneration.

Problem under investigation: surgical repair of complete transection of the spinal cord.

Hypothesis: if the transected spinal cord is provided with a suitable local environment to regenerate, there will be better chances for an anatomical re-connection and a restoration in function.

Description of research methods. First phase: computer-assisted design and 3D rapid prototyping of the device. A Tyrosine-derived polycarbonate will be used as a degradable material. The best possible implant geometry will be tested to fit into the anatomy of the rabbit spinal canal at lower thoracic level. Second phase: a comparative study (twelve animals) of the early phases of spinal cord recovery. Combined MBP and ChAT immunostaining and magnetic resonance tractography will be applied. Third phase: a comparative study (six animals) of the recovery up to 3 months.

Summary of findings (first phase). A tyrosine-derived polycarbonate polymer has been used to fabricate and 3Dprint a two-piece asymmetric device (the “neurobox” concept; Microsurgery 2009;29(4):310-8; J Reconstr Microsurg. 2018;34(6):389-398). A surgical procedure has been developed and initial fitting of the device has been tested in a rabbit cadaver: a bilateral laminectomy is performed at T9 to access the spinal canal. The ventral half of the device encompasses the level of the lesion and it can slip upward and downward over the posterior longitudinal ligament. The dorsal half may be easily adapted to close the canal.

Statement of how the research advances the SCI field: our study will address fundamental mechanisms in spinal cord regeneration and repair. Moreover, it will test a new surgical technique aimed at being translated into clinical practice. This device-assisted procedure can integrate and potentiate the majority of current therapeutic approaches.

Supported by the New Jersey Commission on Spinal Cord Research

(53) NEURAL STEM CELL AND NANOPARTICLE ENCAPSULATION IN MICRORIBBON HYDROGELS IN A TRANSPORTABLE PLATFORM FOR SPINAL CORD INJURY SITE MODULATION AND REPAIR

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Research advancements by multiple international teams emphasize the need for a multicomponent approach to treating spinal cord injury that includes injury site modulation and appropriate cell therapy. Goals to streamline treatments require easy-to-implement platforms that bring uniformity and reproducibility for comparative analysis, optimization and synergy of efforts. Towards this goal we present our findings in designing a biocompatible hydrogel microribbon platform for encapsulation, transport and delivery of therapeutic neural cells- including current analysis with human neural stem cells and future aims with spinal motor neurons and oligodendrocytes- along with supportive maintenance or differentiation needs of therapeutic and supportive cells and nanoparticle modulation of the refractory injury microenvironment. This *dual spinal treatment enhancing platform* (2STEP) approach will deliver cells and promote regenerative repair pathways to reestablish neural connectivity. This work is part of a larger study to address cellular regeneration and repair of SCI by combining stem cell modulation and nanotechnology methodologies in a C4-C5 hemicontusion and behavioral animal model of SCI. The current work presents findings with human neural stem cells in hydrogels. The stem cell work applies published hiPSC lines developed and comprehensively characterized in the Paluh and Cibelli laboratories that are from population diverse sources that include self-defined African American and Hispanic Latino original tissue sources. The collaborative team brings together expertise in pluripotent and neural human stem cell biology, nanotechnology and materials engineering, coupled with additional relevant expertise in the neuronal microtubule cytoskeleton, glycoproteins and extracellular matrix and electrophysiology. The research is part of a 3-year funded project by the New York State Spinal Cord Injury Review Board (NYSCIRB) under the NYS Department of Health DOH-PART2-2017-00067//C33278GG.

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