



Department
of Health



SPINAL
CORD
INJURY
RESEARCH
BOARD

Annual Report

January 1, 2017 to December 31, 2017

I. INTRODUCTION

Spinal cord injury (SCI) was once thought of as incurable. The basic science carried out by researchers in this field, much of it accomplished in New York State, has served as an important stimulus for the clinical trials now underway in fields as diverse as neuro-rehabilitation, axon growth, cell biology and robotics. Although it is not yet possible to reliably repair the human spinal cord, there are new treatments that improve the lives of SCI patients, and continued scientific explorations offer hope for doing more.

SCIs contribute to significant disability, illness and death in the United States. Each year, approximately 1,000 New York residents suffer traumatic SCIs¹ joining the nearly 282,000 people living in the United States who have SCI.² The personal and economic costs to these individuals, their families and society are immense.

Most frequently, these injuries are caused by motor vehicle accidents, falls, sports injuries, or acts of violence. SCI results in an abrupt change in the quality of life for those affected. Injuries to the spine near the head can result in quadriplegia, with the loss of motor control, sensation and function of the arms, legs, bowel, bladder, chest, abdomen and diaphragm. Injuries to the lower spine can result in loss of sensation and movement in the lower body, and loss of bowel and bladder control. Both types of injuries can result in significant chronic pain.

In addition to societal and individual costs incurred for medical care and through loss of productivity, there are significant costs for home and vehicle modifications, equipment purchase, medications and personal assistance services. The National Spinal Cord Injury Statistical Center reported that first-year costs for an individual with SCI range from approximately \$352,279 to more than \$1,079,412, with annual costs thereafter ranging from approximately \$42,789 to \$187,443². These expenses are borne by the individuals, their families and society at large.

The New York State Spinal Cord Injury Research Board (SCIRB) was created in 1998 to solicit, review and support proposals from leading New York State researchers in their efforts to find a cure for SCI. The Spinal Cord Injury Research Trust Fund (Trust Fund) was established to fund this research. It is financed primarily by a portion of surcharges on moving traffic violations, because motor vehicle accidents are the leading cause of SCI, followed by falls.² The SCIRB and Trust Fund are authorized by Title IV (Sections 250 through 251) of Article 2 of the Public Health Law and Section 99-f of Article 6 of the State Finance Law.

The SCIRB first convened in August 1999. The SCIRB is required to report annually to the Governor and Legislature on funds appropriated for SCI research and the progress of the SCIRB in terms of the results of its SCI research efforts.

¹ New York State Department of Health, Bureau of Occupational Health and Injury Prevention, 2012-2014 data

² "Spinal Cord Injury Facts and Figures at a Glance." *National Spinal Cord Injury Statistical Center*. University of Alabama at Birmingham, 2017. Web. 18 August 2017. <https://www.nscisc.uab.edu/>

The SCIRB's mission and goal is to:

1. Seek major advances toward a cure and not simply incremental gains or incremental improvements for SCI patients
2. Support research that tests novel hypotheses and/or advances innovative research approaches that could move the field of SCI research significantly forward toward discovering a cure for SCI.

The SCIRB's mission is to stimulate high-quality, innovative SCI research that will help promote treatment and cure for SCI, including methods for reversing paralysis or restoring function caused by injury, or for minimizing or preventing damage occurring during acute phases of injury. To achieve this mission, the SCIRB advises the New York State Department of Health Extramural Grants Administration Program regarding funding opportunities for competitive research awards to support New York State scientists and their collaborators from a variety of biomedical disciplines.

The SCIRB is responsible for advising the Commissioner of Health on research proposals from leading New York State researchers in their efforts to find a cure for SCI. Information about the SCIRB can be found at: <http://www.wadsworth.org/extramural/spinalcord.htm>.

The SCIRB appreciates the opportunity to serve the citizens of New York State by focusing on this important public health problem while stimulating economic growth through scientific research, investigation and discovery. The SCIRB looks forward to providing additional financial support for such highly meritorious SCI research in the coming years.

II. SCIRB ORGANIZATION AND MEMBERSHIP

The SCIRB is comprised of 13 members appointed by the Governor and legislative leaders (see [Appendix 3](#)). There are two vacancies. The current composition of the SCIRB includes seven researchers, two clinicians and two spinal cord-injured persons. Members serve four-year terms.

III. SCIRB OPERATIONS

Meetings

Meetings are announced at least two weeks in advance whenever possible and are open to the public. Meeting agendas are posted on the Wadsworth Center's web site at: <http://www.wadsworth.org/extramural/spinalcord/meetings>.

A recording of each meeting is available via the Department of Health's public web site <http://www.health.ny.gov/events/webcasts/archive/> for 30 days after a meeting, opening the proceedings to a wide audience.

All SCIRB meeting agendas and approved minutes are available by request from the SCIRB's Executive Secretary.

The SCIRB held two meetings in 2017 (see [Section IV](#), below).

Bylaws

No changes were made to the SCIRB's bylaws in 2017. The bylaws can be found at <http://www.wadsworth.org/extramural/spinalcord/advisory-board/statutes-bylaws>.

IV. MAJOR ACTIVITIES OF THE SCIRB

In fiscal year (FY) 2017, \$8.5 million was programmed to support SCI research.

At its January 18, 2017 meeting, the SCIRB met and recommended funding for two (2) Predoctoral and seven (7) Postdoctoral awards from the "Individual Predoctoral and Postdoctoral Fellowships in SCI (Round 2)" RFA, for a total of \$1.5 million. These are three-year awards and contracts began in September 2017. A tabular summary of this procurement can be found in [Appendix 1](#).

At its September 26, 2017 meeting, the SCIRB met and recommended funding for 14 awards from the "Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activities (IDEA) in Spinal Cord Injury" (Round 2) RFA for a total of \$6.5 million. These are three- and two-year awards respectively. Also, the SCIRB recommended funding for two (2) awards from the "Translational Research Projects (TRP) in Spinal Cord Injury" (Round 2) RFA for a total of \$2.8 million. Tabular summaries of these procurements can be found in [Appendix 1](#).

The SCIRB also approved the release of the Individual Predoctoral and Postdoctoral Fellowships in Spinal Cord Injury (Round 3) RFA for \$1.5 million available for six (6) awards. Applications were due on October 5, 2017. The SCIRB will meet to vote on these applications in 2018 and awards will be featured in the 2018 SCIRB Annual Report.

Previously Recommended SCI Research Contracts

In January 2017, eleven (11) contracts for the PART and IDEA (Round 1) began. The scientific progress resulting from these multiyear awards can be found in [Appendix 2](#).

In March 2017, the Solicitation of Interest for Support of Current Peer-reviewed Spinal Cord Injury Research in New York State (Round 6) contracts began. This opportunity made SCI research funds available to organizations located within New York State that demonstrated a current notice of funding award or renewal from a peer-reviewed SCI research project conducted by a principal investigator employed at their organization. Twenty (20) five-year awards were approved to provide additional support for SCI research projects through the purchase of laboratory supplies, salaries, equipment and other customary expenses necessary to support research efforts. The scientific progress resulting from these SCI funded projects can be found in [Appendix 2](#).

In March 2017, five (5) Individual Predoctoral and Postdoctoral Fellowships in Spinal Cord Injury Research (Round 1) contracts completed their second year. The scientific progress resulting from these three-year awards can be found in [Appendix 2](#).

By August 2017, two (2) Translational Research Projects in Spinal Cord Injury (Round 1) contracts completed their first year. The scientific progress resulting from these five-year awards can be found in [Appendix 2](#).

By the end of 2017, three (3) Collaborations to Accelerate Research Translation (CART) contracts completed their second year and six (6) IDEA contracts completed their final year. The scientific progress resulting from these three- and two-year awards, respectively, can be found in [Appendix 2](#).

Appendix 1

2017 Individual Predoctoral and Postdoctoral Fellowships in SCI (Round 2) Recommendations for Award

Organization	Investigators	Funding Mechanism	Project Title	Recommended Award
Bronx Veterans Medical Research Foundation, Inc	Noam Harel, M.D., Ph.D. Yu-Kuang Wu, P.T., Ph.D, Fellow	Postdoctoral Fellowship	EMG Triggered Closed-Loop Stimulation for Spinal Cord Injury Individuals	\$187,440
Columbia University	Sunil K. Agrawal, Ph.D. Dario Martelli, Ph.D., Fellow	Postdoctoral Fellowship	Improving locomotor function after spinal cord injury with a perturbation-based balance training	\$193,482
Cornell University	Chris B. Schaffer, Ph.D. Yu-Ting Chen, Ph.D. Student, Fellow	Predoctoral Fellowship	In vivo three-photon excited fluorescence imaging of spinal cord neural activity in awake, locomoting mice after spinal cord injury	\$135,600
Feinstein Institute for Medical Research	Ona Bloom, Ph.D. Nawshin Kutub, Ph.D., Fellow	Postdoctoral Fellowship	Biomarkers in adult and pediatric traumatic spinal cord injury	\$168,414
Icahn School of Medicine at Mount Sinai	Hongyan Zou, Ph.D., M.D. Shalaka D. Wahane, Ph.D., Fellow	Postdoctoral Fellowship	Epigenetic modulation of immune response to enhance neuroprotection in spinal cord injury	\$176,550
Rensselaer Polytechnic Institute	Ryan J. Gilbert, Ph.D. Anthony D'Amato, Ph.D. Student, Fellow	Predoctoral Fellowship	Estrogen based biomaterials promote astrocytic growth factor production and provide neuroprotection against glutamate excitotoxicity	\$135,600

Organization	Investigators	Funding Mechanism	Project Title	Recommended Award
University of Rochester	Christoph Proschel, Ph.D. Jennifer Stripay, Ph.D., Fellow	Postdoctoral Fellowship	Novel pharmacological approach to promoting myelin preservation, neuronal regeneration and preventing muscle atrophy following SCI	\$176,454
Winifred Masterson Burke Medical Research Institute	Caitlin E. Hill, Ph.D. Ying Dai, Ph.D., Fellow	Postdoctoral Fellowship	Improving axonal growth through Schwann cell transplant by the activation of integrin following SCI	\$174,090
Winifred Masterson Burke Medical Research Institute	Edmund R. Hollis, Ph.D. Yue Li, Ph.D., Fellow	Postdoctoral Fellowship	Motor learning mechanisms during rehabilitation from spinal cord injury	\$168,414
Total (9 awards)				\$1,516,044

2017 PART/IDEA (Round 2) Recommendations for Award

Organization(s)	Investigator(s)	Funding Mechanism	Project Title	Recommended Award
Applicant: Bronx Veterans Medical Research Foundation Subapplicant: Icahn School of Medicine at Mount Sinai	PI: Christopher Cardozo, M.D. Co-PI: Dongming Cai, M.D., Ph.D. Subapplicant Staff: Bin Zhang, Ph.D.	IDEA	Role of Synaptojanin 1 in Functional Recovery after Spinal Cord Injury	\$344,624
Applicant: Bronx Veterans Medical Research Foundation	PI: Jill Wecht, Ed.D.	IDEA	Dose Effect of Norepinephrine Precursor (Droxidopa) on Blood Pressure and Cerebral Blood Flow Velocity in Hypotensive Individuals with Spinal Cord Injury	\$344,887
Applicant: Icahn School of Medicine at Mount Sinai	PI: Hongyan Jenny Zou, M.D., Ph.D.	IDEA	Enhancing Axon Regenerative Capacity Through Epigenetic Regulation of DNA Methylation Dynamics	\$360,000
Applicant: Regenerative Research Foundation Subapplicant: Marine Biological Laboratory	PI: David Butler, Ph.D. Subapplicant Staff: Jennifer Morgan, Ph.D.	IDEA	Developing Intracellular Antibodies Against Alpha-Synuclein as Potential Therapeutics in Spinal Cord Injury and Disease	\$311,921
Applicant: Regenerative Research Foundation Subapplicant: The Children's Hospital Corporation	PI: Sally Temple, Ph.D. Subapplicant Staff: Larry Benowitz, Ph.D.	IDEA	The Role of Zinc in Axon Regeneration Following Spinal Cord Injury	\$335,000

Organization(s)	Investigator(s)	Funding Mechanism	Project Title	Recommended Award
Applicant: Research Foundation for SUNY - SUNY Polytechnic Institute Subapplicant: The Methodist Hospital Research Institute	PI: Janet Paluh, Ph.D. Subapplicant Staff: Philip Horner, Ph.D.	PART	Healing the Contusion-Injured Spinal Cord Microenvironment with Nanotechnology- and Stem Cell- Assisted Modulation	\$970,404
Applicant: The Feinstein Institute for Medical Research Subapplicant: Bronx Veterans Medical Research Foundation	PI: Ona Bloom, Ph.D. Subapplicant Staff: Ann Spungen, Ed.D.	IDEA	Impact of Walking on the Immune System of Persons with Chronic Spinal Cord Injury	\$222,870
Applicant: The Research Foundation of CUNY obo City College of New York Subapplicant: The Trustees of Columbia University in the City of New York	PI: John Martin, Ph.D. Subapplicant Staff: Sunil Agrawal, Ph.D.	IDEA	Robotic Rehabilitation to Promote Recovery of Forelimb Function after Cervical SCI in Rats	\$332,738
Applicant: The Research Foundation of CUNY obo College of Staten Island Subapplicant: Bronx Veterans Medical Research Foundation	PI: Maria Knikou, P.T., Ph.D. Subapplicant Staff: Noam Harel, M.D., Ph.D.	PART	Activity-Dependent Transspinal Stimulation for Recovery of Walking Ability after SCI	\$898,595
Applicant: University of Rochester	PI: Mark Noble, Ph.D.	PART	Acute Treatment with 4-aminopyridine Promotes Extensive Recovery from Traumatic SCI	\$990,000

Organization(s)	Investigator(s)	Funding Mechanism	Project Title	Recommended Award
Applicant: Winifred Masterson Burke Medical Research Institute	PI: Jason Carmel, M.D., Ph.D.	IDEA	Combining 4-AP with Motor Training to Promote Forelimb Motor Recovery in Rats with Pyramidal Tract Injury	\$359,241
Applicant: Winifred Masterson Burke Medical Research Institute	PI: John Cave, Ph.D.	IDEA	Molecular Mechanisms Regulating Cell Adhesion in Reactive Astrocytes and Glial Scar Formation Following Spinal Cord Injury	\$360,000
Applicant: Winifred Masterson Burke Medical Research Institute Subapplicant: University of Michigan	PI: Edmund Hollis, Ph.D. Subapplicant Staff: Roman Giger, Ph.D.	IDEA	Immune-mediated Nervous System Repair	\$360,000
Applicant: Winifred Masterson Burke Medical Research Institute	PI: Jian Zhong, Ph.D.	IDEA	Investigating Axonal mRNA Translation in CST Axon Sprouting and Regeneration	\$360,000
Total (14 awards)				\$6,550,280

2017 TRP In Spinal Cord Injury (Round 2) Recommendations for Award

Organization(s)	Investigator(s)	Project Title	Recommended Award
Applicant: Health Research Inc. Subapplicant: Medical University of South Carolina	PI: Jonathan Wolpaw, M.D. Co-PI: Gerwin Schalk, Ph.D. Subapplicant Staff: Aiko Thompson, Ph.D.	A Spinal Reflex Operant Conditioning System Suitable for Clinical Translation	\$1,623,620
Applicant: University of Rochester	PI: Mark Noble, Ph.D. Co-PI: Christoph Proschel, Ph.D.	Pharmacological Treatment of Acute Spinal Cord Injury	\$1,203,455
Total (2 awards)			\$2,827,075

Appendix 2

Scientific Progress Resulting from Spinal Cord Injury Research Board-Funded Projects

PART/IDEA (Round 1)

IDEA Contract Term 1/1/17-12/31/18; PART Contract Term 1/1/17-12/31/19

**Progress Reporting Period
1/1/17-6/30/17**

11 Awards, Procurement Total: \$6,264,035

1. Bronx Veterans Medical Research Foundation, Peters VA

Principal Investigator: Hesham Tawfeek, M.D.

IDEA: \$356,999

Project Title: Role of T cells in Bone Loss After Spinal Cord Injury

Introduction/Background: Bone loss after SCI is a major clinical problem due to the high incidence, severity, resistance to treatment, and the subsequent bone fracture. This project investigates a possible role of T cells of the immune system in bone loss after SCI. Therefore, mice that have or lack T cells undergo sham (control) or SCI surgery and bone loss is measured after one, two, or five weeks after surgery. Additionally, changes in T cell subsets, factor secretion, gene expression, and T cell interaction with other bone cells are assessed. The studies may shed light into a possible interaction between the immune system and the skeleton and could have important implications for reducing the risk of bone fracture in SCI. In the first and second quarters of the study, researchers aimed to examine the role of T cells in bone loss after one and two weeks of SCI.

Progress Toward Specific Aims: Researchers have achieved significant progress toward addressing the role of T cells in bone loss after SCI. During this period, a few of the planned experiments have been performed and the analysis of isolated samples is ongoing.

Future Directions: Researchers plan to move forward with the experiments as outlined in the original proposal. Results will be analyzed and reported in future progress reports.

Impact: The success of the SCI surgery in the immune deficient animals is considered a major step toward achieving the proposed aims of the study. Researchers anticipate that by the next reporting period, they will have more results that would help anticipate the impact of the proposed experiments.

2. Cornell University

Principal Investigator: Chris B. Schaffer, Ph.D.

IDEA: \$350,876

Project Title: Imaging Neural Activity in the Spinal Cord of Awake Mice After Spinal Cord Injury

Introduction/Background: The goal of this project is to develop the capability to directly image the patterns of neural activity in the spinal cord of mice before and after SCI. Such a capability would enable researchers to uncover the changes in activity patterns in the spinal cord neurons that control limb motion after a SCI.

Progress Toward Specific Aims: Researchers aim to develop the capabilities to image neural activity patterns in genetically-defined sub-populations of neurons in the spinal cord during mouse locomotion. They will investigate how these activity patterns change after an upstream SCI. Significant progress has been made including the demonstration of imaging at sufficient depth in the spinal cord to study the relevant neurons, demonstration of imaging of neural activity in the spinal cord, and successful targeting of the fluorescent reporters of neural activity to a genetically defined sub-population of neurons.

Future Directions: Researchers will focus on two primary tasks. First, they will integrate their mouse limb motion tracking system with the microscope to image neural activity. Second, they will begin measuring neural activity during locomotion in the sub-population of neurons that they have successfully targeted the activity reporters to.

Impact: This work will use their recently developed capability to image neural activity in the spinal cord of awake, spine-fixed mice moving on a treadmill to investigate altered patterns of activity in a genetically defined set of spinal cord neurons after upstream SCI and correlate those changes with changes in hindlimb motion.

3. Research Corporation of Long Island, Inc., Northport VA

Principal Investigator: Victor L. Arvanian, Ph.D., D.Sci

Sub-applicant: Houston Methodist Research Institute

PART: \$935,867

Project Title: Neuroplasticity Integrating Human Induced Neuralized Pluripotent Stem Cells (NiPSCs) in SCI Animals

Introduction/Background: Recent studies from the Center for Neuroregeneration, Department of Neurosurgery, Houston Methodist Neurological Institute, led by Philip J. Horner, Ph.D., revealed that Neural Progenitor Cells (NPCs), derived from NiPSCs can be reprogrammed to become neurons and oligodendrocytes with an ability for good survival and integration in the chronically injured spinal cord of adult rats.

Based on results of recent experiments, conducted in the laboratories of Victor L. Arvanian, Ph.D., D.Sci and Dr. Horner, we hypothesize that spinal electro-magnetic stimulation (sEMS) and exercise combined with transplantation of NiPSCs may improve incorporation of NiPSC-derived neurons into host spinal cord and promote formation of new functional synaptic connections to neurons in the damaged spinal cord.

Progress Toward Specific Aims: Researchers conducted a control experiment to examine if NiPSCs cells remain functional after implantation into damaged spinal cord. 10 rats received contusion SCI and were implanted with NiPSCs immediately after injury, then randomly divided into two groups. Group 1 received sEMS followed by exercise training. Group 2 received NiPSCs and only control treatments. All rats receive immunosuppressant cyclosporine daily during survival period of six weeks to maximize survival rate of implanted NiPSCs. Locomotion of all rats is being assessed weekly.

Overall all rats exhibit no any adverse effect from NiPSCs implantation. The experiment is on-going and the results will be analyzed.

Future Directions: Researchers will conduct the experiment as described above but will implant NiPSCs at two and six weeks post injury.

Impact: This triple combination treatment (NiPSCs, sEMS and exercise) carries the potential for developing a novel, feasible and effective translational set of treatments for acute and chronic contusion SCI. During this reporting period, researchers have begun their first experiment. They will conduct a behavioral assessment as well as electrophysiological and immunochemical investigations; results will be analyzed and reported in future progress reports.

4. Research Foundation for SUNY Stony Brook

Principal Investigator: Sue Ann Sisto, Ph.D.

PART: \$989,199

Project Title: Effects of Spinal Electromagnetic Stimulation and Locomotor Training on Motor Recovery and Walking in Incomplete SCI

Introduction/Background: The objective is to examine the potential effects of sEMS and Locomotor Training (LT) exercise on the spinal, cortical circuits and the recovery of motor and physical function in adults with incomplete SCI. This stimulation will first be provided to healthy individuals to determine the ideal parameters and expectations for SCI testing and training.

Progress Toward Specific Aims: After several submissions to the Institutional Review Board (IRB), researchers have received IRB approval for the first phase of the study to test healthy individuals. They have acquired and set up the necessary equipment to conduct neurophysiological testing, sEMS and transcranial electrical stimulation. Researchers have developed a detailed manual of procedures for screening and testing that they have practiced repetitively to ensure efficiency and safety of testing and training procedures. They have enlisted a neurologist to assist with screening, monitoring, developing detailed data sheets, data back-up and security to ensure data integrity, and hired an exercise professional and physical therapist.

Future Directions: Researchers will begin testing their eight (8) healthy participants using sEMS, and monitor motor and sensory evoked potentials. Each participant will receive three (3) sessions with the goal of identifying idealized set-up and parameters. After set-up and parameters are established, they will introduce sEMS on healthy and incomplete SCI participants for several weeks, and a combination of sEMS with LT. Finally, they will interview and hire a post-doctoral fellow.

Impact: Careful data collection of healthy non-injured humans will set the stage for idealized data collection in humans with SCI.

A citation that has been accepted as a result of this funding is listed below:

Arvanian, V. L., Petrosyan, H. A., Sisto, S. A., & Kaufman, M. (2017). *Non-invasive Electromagnetic Stimulation of Neuro-muscular Circuitry: Translating from Animal Research to Clinic*. Poster presented for the Spinal Cord Injury: Animal Models and Human Studies Session, Society for Neuroscience Meeting, Washington, D.C.

5. Research Foundation for SUNY Stony Brook

Principal Investigator: Irene C. Solomon, Ph.D.

IDEA: \$355,111

Project Title: Therapeutic Potential of Mild to Moderate AIH on LUT and Respiratory Function in SCI

Introduction/Background: SCI results in reduction or loss of motor, sensory, and autonomic function below the level of the injury. Research aimed at enhancing functional recovery following SCI is essential, and exposure to acute intermittent hypoxia (AIH; single and repeated bouts (rAIH)) has been shown to elicit functional improvements in spinal motor systems in rats and humans following incomplete SCI. This project investigates the effects of mild to moderate AIH (SA1) and the therapeutic potential of rAIH exposure (SA2) to improve lower urinary tract (LUT) and respiratory motor dysfunction following SCI.

Progress Toward Specific Aims: Researchers have conducted experiments assessing LUT and respiratory motor activities in response to single bout moderate AIH exposure in both uninjured (naïve and SCI sham) and moderate contusion SCI (4-week survival) rats. In SCI rats before AIH exposure, pronounced rhythmic bladder activity consisting of both non-voiding and voiding bladder contractions was observed; few or no non-voiding bladder contractions were seen in uninjured rats. Following AIH exposure, an improved pattern of bladder activity characterized by fewer non-voiding bladder contractions, increased voiding volume, and emergence of a threshold-driven pattern of bladder contraction (characteristic of that seen in uninjured rats) was observed in SCI rats. In uninjured rats, a decrease in voiding frequency with increased voiding volume was also noted post-AIH. These observations suggest that AIH is capable of modulating/improving LUT function in SCI (and uninjured) rats.

Future Directions: Researchers plan to complete experiments proposed in SA1 during the remainder of 2017, and then begin experiments proposed in SA2 (scheduled to begin in 2018).

Impact: Researchers have implemented a promising non-invasive therapeutic approach to facilitate LUT and respiratory recovery following SCI. This therapeutic strategy, which can be integrated into clinical use in various settings (e.g., hospital, rehabilitation center, home), would exert a significant positive impact on quality of life in SCI patients.

6. Research Foundation for SUNY, University at Albany

Principal Investigator: Ben G. Szaro, Ph.D.

IDEA: \$359,738

Project Title: Functional Analysis of Genes Implicated in Successful CNS Axon Regeneration

Introduction/Background: The tremendous progress made toward understanding why central nervous system (CNS) axon regeneration fails in mammals has underscored the need for combinatorial therapeutic strategies. Studying animal models, such as the frog *Xenopus laevis*, where successful CNS axon regeneration occurs naturally can provide a rational basis for designing such strategies. Frogs are one of the best models for such studies, because they recover from SCI as tadpoles but not as frogs, and because they recover from optic nerve injury throughout life. Earlier studies have identified a gene [heterogeneous ribonucleoprotein K (hnRNP K)] that is required for regulating

expression of structural proteins required to make axons, and additional genes that are differentially expressed in tadpole vs. frog hindbrain after SCI. The first objective tests whether hnRNP K and its regulators help determine success or failure of CNS axon regeneration. The second objective tests the functions of differentially expressed genes identified in from the earlier microarray study of hindbrain under regeneration permissive versus regeneration inhibitory conditions.

Progress Toward Specific Aims: In the first six months of the project, efforts were targeted at hiring personnel and gathering the reagents and tissue samples needed to carry out the specific aims. Microarray data from the earlier studies was compared with new data RNA-seq data (generated from the Institutional Support for SCI Research Award, Round 5), which are now available from the *Xenopus* genome to identify the precise gene homeologs that are differentially expressed between regenerating vs non-regenerative CNS tissues (e.g., tadpole hindbrain and frog eye versus frog hindbrain) after injury. The early stage of the analysis has pointed to the S. homologs of the MORC3 (microrchida 3) gene as the most interesting candidate for functional studies.

Future Directions: Efforts during the next reporting period will be targeted toward identifying cell types in the injured hindbrain and retina that undergo changes in both the differentially expressed genes (e.g, MORC3.S), as well as in the regulators of hnRNP K. Once those studies are complete, appropriate functional experiments will then be performed to determine how these genes function during CNS axon outgrowth.

Impact: Successful completion of these objectives will provide new information which could ultimately lead to new therapies for treating SCI in humans. Important questions will be answered such as, "Why CNS axon regeneration succeeds in some instances and fails in others?" Such information is key to developing rational approaches for CNS axons to regenerate in mammals.

7. The Research Foundation of CUNY obo College of Staten Island

Principal Investigator: Maria Knikou, P.T., Ph.D.

PART: \$947,004

Project Title: Transspinal-Transcortical Paired Stimulation for Neuroplasticity and Recovery After SCI

Introduction/Background: The focus of the research project is to delineate the neuromodulatory and rehabilitative effects of non-invasive combined brain and spinal stimulation at rest and during robotic gait training in people with motor incomplete spinal cord injury (iSCI) and in healthy control subjects. Stimulation over the primary motor cortex and thoracolumbar spinal cord is delivered daily for 40 minutes in a paired paradigm protocol when participants are lying on their back and during body weight support robotic assisted step training at specific phases of each step cycle. Before and after 15 sessions of each intervention, cortical, corticospinal, and spinal neural excitability via non-invasive neurophysiological methods and recovery of motor function via clinical tests in people with iSCI are established.

Progress Toward Specific Aims: All procedures for purchase and finance of the Lokomat have been completed and two postdoctoral research fellows will start in September 2017. Researchers have advertised the research study in several media platforms, and they have at least 70 people with SCI in the patient registry who have expressed their interest to participate in the research study. Currently, they are establishing eligibility to

ensure that all procedures are safe for everyone. Further, in seven (7) healthy control subjects, researchers assessed the effects of non-invasive thoracolumbar transspinal stimulation on the soleus H-reflex modulation pattern during walking on a motorized treadmill. Last, they developed all hardware and software arrangements for stimulation delivery during robotic gait assisted stepping, and data analysis.

Future Directions: Efforts during the next year include continuous recruitment of people with SCI, enroll and complete experiments and 15 stimulation sessions for Aim 1 and Aim 2 in 12 control subjects and 12 SCI subjects (e.g. test one control and two SCI subjects every month). Data analysis will be performed during completion of post-intervention measurements, but manuscripts from both subject groups will be submitted for publication when all sessions are completed, so a pre-post stimulation statistical analysis can be performed.

Impact: Transspinal-transcortical paired stimulation, in people with and without SCI, delivered in the supine position and during assisted stepping is a novel neuromodulation method to induce neuroplasticity and improvements in motor function and abnormal muscle tone. The results may change the rehabilitative approaches of people with SCI. Results from this research study will provide evidence on physiological and behavioral changes following paired transspinal and transcortical stimulation on neural circuits susceptible to plasticity.

8. The Trustees of Columbia University in the City of New York

Principal Investigator: Ulrich Hengst, Ph.D.

IDEA: \$360,000

Project Title: Pumilio 1 and 2 Control Axon Regrowth by Shaping the Axonal Transcriptome

Introduction/Background: Axon regrowth following injury is controlled by cell intrinsic and extrinsic factors. One of the most important cell intrinsic determinants of axon growth is the production of new proteins. While the bulk of protein synthesis occurs in the neuronal cell bodies, the injured axons themselves are also able to produce proteins locally. In their previous studies, researchers identified a pair of proteins that control which mRNAs are localized to and translated within axons. By modulating the abundance of these proteins in neurons, they have been able to greatly reduce or increase the ability of axons to grow.

In this research project, researchers will elucidate the mechanism behind these effects and determine which proteins' local production is responsible for the increased or reduced capacity of axons to regrow following injury.

Progress Toward Specific Aims: Researchers have focused their research efforts on establishing the role of Pumilio-2 in regulating the intrinsic growth capacity of injured axons. They created Lentiviruses for knocking down Pum2 and Pum1 expression by shRNA and validated their efficacy. They confirmed that the effect of Pum2 knock-out on axonal growth and regeneration, and quantification of axonal growth rates in neurons with and without Pum2 expression is ongoing. They evaluated the expression and axonal localization of additional mRNAs, that might be Pumilio targets, and observed phenotype of Pum2 or Pum1 knockout neurons to establish the optimal conditions for the transcriptome analysis. They identified that phosphatase and tensin homolog

(PTEN), a tumor suppressor gene, is a major intrinsic regulator of axonal growth, both during the development and in injured axons.

Future Directions: Researchers will include PTEN and fluorescence in situ hybridization (FISH) in the analysis of changed Pumilio expression in injured axons to confirm that PTEN is a major intrinsic regulator of axonal growth, both during development and in injured axons. If Pum2 is indeed an intrinsic regulator of PTEN expression, as the data suggests, it could present a novel avenue to target this key regulator of growth in injured axons.

Impact: The successful completion of this project will provide a mechanistic understanding of the role of the mammalian Pumilio homologs, Pum1 and Pum2, in shaping the axonal transcriptome by regulated mRNA degradation and mRNA localization in regenerating axons. These findings will provide the scientific basis for the development of new avenues and targets aimed at improving functional recovery after SCI by targeting axon regeneration.

9. Weill Medical College of Cornell University

Principal Investigator: Anthony Sauve, Ph.D.

Sub-applicant: Winifred Masterson Burke Medical Research Institute

PART: \$890,241

Project Title: NAD-Augmenting Agents to Enhance Neural Survival and Function Following Spinal Cord Injury

Introduction/Background: SCI is a debilitating condition that causes long-term health consequences, such as paralysis, loss of limb function, loss of work, and decline in quality of life. The current set of proven useful pharmacologic approaches to prevent long-term loss of physiologic and functional performance in people with SCI is limited. There is opportunity to intervene to prevent loss of spinal cord neurons and axons and potentiate preservation of function at the earliest receipt of medical care following SCI. A key factor for preservation of neurons and axons is the metabolic co-factor nicotinamide adenine dinucleotide (NAD), suggesting that one possible strategy of intervention is to preserve NAD levels in injured neurons. Researchers seek to evaluate nicotinamide riboside (NR), a nucleoside precursor of NAD⁺, and a variant of NR called dihydro-NR (DHNR) in treatment of SCI, using a rat thoracic contusion model of SCI.

Progress Toward Specific Aims: One of the goals is to evaluate the pharmacokinetic and pharmacodynamic (PK and PD) for NR and DHNR in uninjured and SCI animals. Researchers have synthesized 100 grams of NR and during the current reporting period, they administered NR at escalating doses in uninjured animals. For PK studies, blood has been collected from animals at various time intervals following intraperitoneal injection (IP) injection. For PD studies, tissue samples have been collected from animals at various time intervals. NAD assays for several time points and several tissues have been conducted to assess the pharmacodynamic effect. Assay development for quantitative measurement of NR by High Performance Liquid Chromatography (HPLC) and Mass Spectrometry (MS) is ongoing.

Future Directions: Samples collected from uninjured animals will be finalized, and PK/PD measurements will be completed in the next reporting period. In addition, samples will be collected from SCI animals for PK/PD measurements. This task is expected to be complete during the next reporting period.

Impact: These studies are crucial to determine the dosing and duration of effect time for NR and DHNR in preparation for further administration of NR and DHNR in SCI animal models. The current studies lay the scientific framework to establish optimal dosing and PD effect for the intended studies.

10. Winifred Masterson Burke Medical Research Institute

Principal Investigator: Dylan J. Edwards, Ph.D., P.T.

Sub-applicant: Massachusetts Institute of Technology

IDEA: \$359,000

Project Title: Improving Hand Function in Chronic SCI with Combined Robot Training and Transcranial Direct Current Stimulation

Introduction/Background: SCI typically occurs in young adulthood and often results in incurable paralysis and disability that profoundly affects quality of life of the injured. Interventions for improving hand function yield modest results at best. The pilot data in chronic incomplete SCI, showed that transcranial direct current stimulation (tDCS) over the hand area of the brain, or a regimen of upper extremity robotic training, can improve voluntary movement control of the hand or arm respectively. Here they aim to study the combination of tDCS and robotic training on functional outcome. Participants will undergo robotic hand training (multiple times per week for six (6) weeks), preceded by application of tDCS (or sham tDCS).

Progress Toward Specific Aims: Researchers have successfully developed and submitted the IRB application. They have prepared the different clinical laboratory spaces for each study component, reviewed testing procedures, serviced robotic equipment and upgraded software. They have also marketed the study to prospective participants and clinicians, through multiple approaches, including brochures and the establishment of an IRB-approved registry for patients (including New York Presbyterian/Columbia University Medical College-Weill Cornell Medical College and the Burke Rehabilitation Hospital). They have identified and trained staff and anticipate the first cohort study will begin in September 2017.

Future Directions: Researchers expect to have completed the intervention period for two full cohort studies in 2017, and thus will be on track for study recruitment leading into 2018, with full enrollment ceasing in the fall of 2018 and final data analysis by the end of 2018.

Impact: To date researchers have made their new IRB-approved, NYS funded study, available to community dwelling SCI patients. Participation involving a six (6)-week robotic training regimen, will be of no cost to 30 eligible participants.

A research article that has been published as a result of this funding is listed below: Cortes, M., Medeiros, A., Gandhi, A., Lee, P., Krebs, H., Thickbroom, G., & Edwards, D. J. (2017). Improved grasp function with transcranial direct current stimulation in chronic spinal cord injury. *NeuroRehabilitation*, 41(1), 51-59. doi:10.3233/NRE-171456.

11. Winifred Masterson Burke Medical Research Institute

Principal Investigator: Jian Zhong, Ph.D.

IDEA: \$360,000

Project Title: Visualizing New Synapses and Their Activity in the Injured Spinal Cord

Introduction/Background: To overcome paralysis after SCI, injured axons must regenerate and then form synapses to reconnect with target cells. Very little is known about synapse formation in the injured spinal cord because there is no known way to observe such synapses as they form and mature. Their objective is to express a novel anterograde transsynaptic tracer in corticospinal motoneurons (CSMNs), and observe it moving from CSMNs to spinal interneurons as new synapses form after injury. If researchers can thereby prove that new synapses are formed, they can then determine whether these synapses are active when a SCI mouse moves. Upon completion of this project, new tools will be available to study synaptogenesis, and they will be able to devise ways to accelerate and improve synaptogenesis after SCI.

Progress Toward Specific Aims: Researchers have been breeding the genetically modified mice necessary for the experiment. Since these mice will harbor at least four different genetically modified alleles, researchers will need three rounds of breeding.

They have carried out several surgeries implanting optic windows into the back of the spine with the goal to optimize the technical procedure and maximize optical depth resolution into the spinal cord.

Future Directions: Researchers expect to start the three-photon microscopy imaging of the tracer and Ca²⁺ activities in the motor cortex and spinal cord.

Impact: The results from this project will generate entirely novel insights into post-injury synapse formation. This will be essential for the development of novel therapeutic approaches to facilitate the axon and circuit regeneration, and may be especially useful for the evaluation of training/rehabilitation efforts designed to modulate circuit formation in the spinal cord after SCI.

Institutional Support for Spinal Cord Injury Research (Round 6)

Contract Term 3/1/17-2/28/22

**Progress Reporting Period
3/1/17-8/31/17**

20 Awards, Procurement Total: \$4,850,000

1. Albany Research Institute, Inc. - Albany Stratton VA Medical Center

Funding supported Principal Investigator, Dr. Anulf H. Koeppen, M.D. and other personnel, investigating the trophic role of dorsal root ganglia in spinal cord repair. This investigation established an intimate mutually important relationship between sensory input from dorsal root ganglia and the development and maintenance of the spinal cord. Trauma and diseases of the spinal cord, as exemplified by Friedreich ataxia, disrupt connections between sensory fibers and the gray matter of the spinal cord and brain. During development, boundary cap cells provide a permissive or non-permissive barrier between spinal cord and dorsal root ganglia. When disrupted, astrocytes gain access to dorsal roots and axons fail to enter or re-enter the spinal cord.

A research article that has been published as a result of this funding is listed below: Koeppen, A. H., Becker, A. B., Qian, J., Gelman, B. B., & Mazurkiewicz, J. E. (November 2017). Friedreich Ataxia: Development Failure of the Dorsal Root Entry Zone. *Journal of Neuropathology & Experimental Neurology*, 76(11), 969-977.

Funding also supporting Principal Investigator, Dr. Jonathan R. Wolpaw, M.D. and other personnel, continuing the development and validation of software and assessment protocols for comprehensively testing the hypothesis that appropriate operant conditioning of the soleus H-reflex can trigger widespread plasticity that improves locomotion in people with chronic incomplete SCI and can also improve other skills that use the same spinal cord circuitry. This work is advancing capabilities for designing spinal reflex operant conditioning protocols for people with SCI and evaluating their functional impact. Thus, it is guiding the further development and clinical translation of this new noninvasive therapy that can complement other therapies and enhance functional recovery for people with SCI and other neuromuscular disorders.

2. Albert Einstein College of Medicine (AECOM)

Funding was used to upgrade the 4D-spinning disk confocal microscope imaging system gas lasers to solid state-lasers, which are considerably more stable and energy efficient. This upgrade will ensure that the researchers can complete their proposed cell biology studies and characterize with high precision subcellular alterations occurring in neurons with fidgetin-like 2 depletions.

A citation that has been accepted as a result of this funding is listed below: Baker, L., Tar, M., Charafeddine, R., Nacharaju, P., Friedman, J., Suadicani, S., Sharp, D., & Davies, K. (October, 2017). *Fidgetin-like 2, a Novel Microtubule Regulator, can be Targeted to Promote Nerve Regeneration and Improve Erectile Function after Cavernous Nerve Injury*. Presented for the Basic Science Session, 18th Annual Fall Scientific Meeting of Sexual Medicine Society of North America, Inc, San Antonio, TX.

3. Bronx Veterans Medical Research Foundation - James J. Peters VA Medical Center

Funding supported personnel working on the projects entitled, "Precision of Body Composition Measurements in Persons with SCI" and "Subcutaneous Injection and Ultrasonic Dispersion of Cefazolin into Chronic Pelvic-Region Pressure Ulcers in Persons with SCI." These projects are characterized as feasibility, or proof-of-concept, studies. The feasibility data obtained from these projects may develop an appropriate clinical trial that will be submitted for additional funding to support a larger, but more focused, clinical trial. The additional knowledge and insight gained from the work being performed will advance the researchers understanding of the respective conditions being studied in each project.

4. Columbia University

Funding was used to develop two in-house pelvic supported systems for training of human functions:

- Pelvic-assisted walker support system for overground walking and
- Stair-mill system with a Tethered Pelvic Assist Device (TPAD).

Overground walking and stair climbing are important activities of daily living. However, many individuals with neural impairments, especially SCI, have limitations in these activities. The two systems will allow researchers to explore how robotics can be used to facilitate, augment, and train these movements. These systems are being assembled using mechanical and electronic components. Researchers expect that to receive human data, both for overground walking with pelvic assisted walker and stair-mill system. The results of this study will advance current rehabilitation methods for SCI patients and develop innovative solutions to reduce risk of falls for this patient group.

5. Cornell University

Funding was used to support the addition of a deformable mirror to the three-photon excited fluorescence microscope to improve the performance of the microscope. Three photon microscopy has enabled researchers to image tissue and cell structure with micrometer resolution into the spinal cord of a live mouse as well as to image the patterns of neural activity in spinal cord neurons expressing genetically encoded calcium indicators.

Funding supported the engineering of viral vectors that enabled researchers to express genetically-encoded calcium indicators, specifically, genetically-defined populations of spinal cord neurons.

The improvements in their imaging capabilities coupled with the ability to target calcium sensor expression to genetically-defined cells will allow researchers to fully explore the role of different classes of spinal cord interneurons in shaping limb motion as well as exploring how these activity patterns change after SCI.

6. Health Research, Incorporated

Funding supported personnel to develop and validate a new therapeutic method for improving recovery of useful motor function after SCI. The proposed project will explore the therapeutic impact of combining spinal reflex conditioning with locomotor training. The successful demonstration of the enhanced beneficial impact of their combination should lead to translational studies in humans exploring the ability of this combination to enhance recovery of useful motor function after SCI.

Funding also supported personnel in their study of the role of gap junctions between nerve cells and the improper control over the nerve cells that determine activity of the external urethral sphincter muscle during urinary dysfunction caused by SCI.

7. Icahn School of Medicine at Mount Sinai

Funding supported Principal Investigator, Hongyan, Zou, M.D., Ph.D., and other personnel studying the novel molecular mechanisms of immune response in SCI, in particular Plexin-B2 signaling. Plexin-B2 plays an important role in neurodevelopment, but its function in the immune response in the CNS after injury is not understood. Their preliminary data showed a robust upregulation of Plexin-B2 in microglia and macrophages after SCI. Therefore, researchers hypothesize that Plexin-B2 is an important modulator of the innate immune response after SCI. They first compared primary microglia culture of control and conditional knockout (cKO) mice. Second, for in vivo studies, they have conducted dorsal column lesion in Plexin-B2 cKO mice and controls. Researchers are currently in the process of confirming whether in the cKO mice, the immune response failed to confine the tissue injury, resulting in wider spread of neuroinflammation. Their study has the potential of defining Plexin-B2 as a novel therapeutic target for immunomodulation after SCI. The study not only has a strong impact on advancing basic science, but also has translational value of exploring new signaling pathway regulating immune response after SCI.

8. New York University

Funding was used to purchase an Eppendorf 6335000020 Thermal Cycler which is required to generate recombinant DNA products such as expression constructs, complementary DNA, and library preparation for sequencing. These are integral processes to all the scientists' SCI research activities. Funding was also used to procure reagents and personnel that manage lab operations.

A citation that has been accepted as a result of this funding is listed below:
Mazzoni, E. (August, 2017). *Modeling Differential ALS Sensitivity with Stem-cell-derived Spinal and Cranial Motor Neurons*. Presented for the Contribution of Common Variation Session, New York University Nature Conference on Neurogenetics, New York, NY.

9. Regenerative Research Foundation

Funding was used to purchase a Precision Systems And Instrumentation IH-0400 Impactor, a contusion device specifically designed for medical research using rats and mice, which will be used for various SCIRB active and pending awards. Researchers expect to generate data which will be useful in obtaining funding support for further

investigations in SCI and potential treatment for individuals who presently suffer from SCI.

10. Rensselaer Polytechnic Institute

Funding supported personnel working on the projects entitled, “Electrically Induced Changes in Macrophages and their Impact on Neurons,” and “Interplay Between Astrocytes and Macrophages.” Preliminary data from these projects will be used to write future SCI research applications.

Citations that have been accepted as a result of this funding are listed below:
D’Amato, A., Ziemba, A.M., Puhl, D.L., MacEwan, T., Koppes, A., Koppes, R., Lennartz, M., & Gilbert, R.J. (2017). *IL-4 Releasing Biomaterials Reduce Inflammation to Promote Regeneration after Spinal Cord Injury*. Poster presented for the Spinal Cord Injury, Society for Neuroscience Meeting, Washington D.C.

Johnson, C. & Gilbert, R.J. (2017). *The Effect of Fiber Diameter on Astroglial Morphology and Glutamate Transporter Production*. Poster presented for the Spinal Cord Injury, Society for Neuroscience Meeting, Washington D.C.

11. Research Corporation of Long Island, Inc. - Northport VA Medical Center

Funding was used to purchase the equipment listed below for SCI experiments:

- Isoflurane systems with assessors for gas anesthesia during surgeries and recordings.
- Pulse stimulator for electrophysiology experiments.
- Wireless EMG system for electrophysiology records.

Funding has supported personnel examining the effects of new gene therapy. Future experiments will combine adeno-associated virus (AAV) expressing NG2-neutralizing-antibody and repetitive sEMS treatments in order to improve recovery of function following contusion SCI. This research provides a strong foundation for their animal experiments and human studies.

A citation that has been accepted as a result of this funding is listed below:
Petrosyan, H.A., Alessi, V., Sisto, S.A., Kaufman, M., & Arvanian, V.L. (2017). Transcranial Magnetic Stimulation (TMS) Responses Elicited in Hindlimb Muscles as an Assessment of Synaptic Plasticity in Spino-Muscular Circuitry after Chronic Spinal Cord Injury, *Neuroscience Letters*, 642, 37-42. doi: 10.1016/j.neulet.2017.01.065.

12. Research Foundation of CUNY - City College

The goal is to build institutional capacity for cellular and molecular-based approaches to SCI research at the City College of New York (CCNY). Upon execution, the outcomes are expected to lead to demonstration of organotypic and cellular experimental systems, regeneration-associated gene panel and microRNA panel focused on SCI that would be applied for subsequent studies of SCI pathological processes and prospective molecular therapies. Information and tools resulting from the experimental systems and gene panels will be directly applied in designing future SCI applications.

In 2017, a research assistant worked on the regeneration-associated gene and microRNA literature, and the postdoctoral research associate was hired to conduct the laboratory experimental components. Further progress will be included in the 2018 SCIRB Annual Report.

13. Research Foundation of CUNY - Staten Island

Funding was used to purchase an Lokomat 6 Professional which will be used for the PART research project led by Dr. Maria Knikou. For this project, they will deliver transspinal and transcortical paired associative stimulation at rest and during Lokomat gait training in people with SCI.

Funding was also used to support Dr. Zaghoul Ahmend's SCI research to investigate the effects of trans-spinal direct current stimulation (tsDCS) on adult-born spinal cells (endogenous stem cells) following SCI. Researchers expect that tsDCS will affect the composition of the injury site due to its effect on the number and migration of adult-born spinal cord cells. They further expect that tsDCS will induce long-term effects in the pattern of new-born cells proliferation, migration, and fate. Results from their current project will elucidate novel potential treatments for restorative medicine.

14. Research Foundation of SUNY – Albany

Funding was used to purchase a Leica Model CM 1950 Cryostat, which is being used to generate frozen histological sections of retina, hindbrain, and spinal cord after injury for analysis by histochemical procedures. The data generated using this instrument will be disseminated in publications based on this work, and at meeting presentations of the work.

Funding also supported personnel working towards the goal of identifying genetic and epigenetic changes associated with successful recovery from SCI. They will continue progress toward developing the precise conditions needed to carry out ChIP-Seq on *Xenopus* neural tissues. Researchers anticipate that new data will provide a foundation for building new understanding of the molecular genetic mechanisms that permit some CNS neurons to recover function and others to lose this ability after traumatic injury. They hope that this knowledge will enable the design of new therapeutic approaches to reverse this loss in human SCI.

Citations that have been accepted as a result of this funding are listed below:

Belrose, J.L., Sammons, M.A., Gibbs, K.M., & Szaro, B.G. (2017). *Gene Expression Profiling of Optic Nerve and Spinal Cord Injury in Xenopus laevis Reveals a Core Set of Genes Associated with Successful Regeneration of CNS Axons*. Presented at the *Xenopus Resources and Emerging Technologies Meeting*, National Xenopus Resource Center, Woods Hole, M.A.

Choudhary, R.P. & Szaro, B.G. (2017). *Paradoxical mRNA and Protein Expression of Suppressor of Cytokine Signaling 3 (SOCS3) in Successful Optic Axon Regeneration in Xenopus laevis*. Poster presented for the *Spinal Cord Injury, Society for Neuroscience Meeting*, Washington D.C.

Szaro, B.G., Belrose, J.L., Sammons, M.A., & Gibbs, K.M. (2017). *RNA-seq Analysis of Optic Nerve and Spinal Cord Injury in Xenopus laevis Reveals a Core Set of Injury-*

Induced Genes Associated with Successful CNS Axon Regeneration. Poster presented for the Spinal Cord Injury, Society for Neuroscience Meeting, Washington D.C.

15. Research Foundation of SUNY - Downstate Medical Center

Funding supported personnel focused mainly on the primary motor cortex (M1) microcircuits modeling and the analysis of M1 in vivo experimental data.

The project is aimed at elucidating neural coding mechanisms in M1 that can be used to build autonomous bidirectional brain-machine interfaces for SCI patients. Significant progress was made towards the objectives: computational modeling of M1 neural circuits and analysis of M1 in vivo experimental data.

With respect to computational modeling, researchers simulated the inputs from the main cortical and thalamic regions that project to M1, based on recent experimental data from optogenetic mapping studies. They identified two different pathways that activated corticospinal output. The first pathway involved activation of motor-related regions, such as secondary motor cortex; the second pathway was initiated in sensory-related regions, such as somatosensory cortex, which then triggered M1 superficial layers. Additionally, results showed that modulation of HCN channel in corticospinal neurons served as a switch to regulate corticospinal output, and thus could be used as a mechanism to convert motor planning into motor action activity. Thorough analysis of experimental data provided insights into how M1 encoded the value of the reward delivered as well as the expected reward. They concluded that not only did M1 units encode the value of the expected reward but also encoded the error between its predicted reward and the actual reward delivered. This information can be used to build autonomous brain-machine interfaces.

The research supported through this funding provides insights into how information is encoded in the primary motor cortex. The computational model provides a framework to integrate experimental data from multiple experimental studies. This provides a useful tool for researchers in the field, who can use the framework to evaluate hypothesis and guide the design of new experiments.

Citations that have been accepted as a result of this funding are listed below:
Dura-Bernal, S. (2017). *NetPyNE Tool and Multiscale Model of Mouse M1 Microcircuits*. Presentation delivered at the Bernstein Center for Computational Neuroscience Conference, Gottingen, Berlin.

Dura-Bernal, S., Neymotin, S.A., Suter, B.A., Shepherd, G.M.G., & Lytton, W.W. (2017). *Data-driven Multiscale Model of Mouse M1 Microcircuits*. Posted presented at the 26th Annual Computational Neuroscience Meeting, Antwerp, Belgium.

16. Research Foundation of SUNY - Stony Brook

Funding was used to purchase the equipment listed below. This equipment will assist with expanding SCI surgical core facilities, the assessment of spontaneous locomotor and explorative motor behaviors, and performing high throughput biochemical assays.

- Stereotaxic Hardware consisting of small animal frames, electrode carriers, and animal-specific anesthesia masks for securing animals (rats and mice) during SCI surgical interventions.

- PhysioSuite with MouseSTAT Pulse Oximeter and Heart Rate Monitor for noninvasive pulse oximetry and heart rate monitoring of anesthetized rats and mice during surgical SCI interventions.
- PSI IH-0400 Impactor (with user-supplied computer) for generating contusion injuries of the spinal cord in rats and mice.
- Noldus PhenoTyper rat systems for continuous measurement and testing of spontaneous locomotor ability and explorative behaviors in rodents and EthoVision tracking and analysis software for simultaneous monitoring of SCI and control rats.
- Direct Detect Infrared Spectrometer for accurate and direct quantification of total protein in a small volume of sample.
- Luminex200 for measurement of multiple protein biomarkers simultaneously in a sample.

While the equipment identified above has been recently purchased and/or received, installation and training are pending for some of the instruments.

For the purchase of the Luminex200 and Direct Detect Infrared Spectrometer, researchers received matching funds from Stony Brook University School of Medicine and the Research Foundation of SUNY. These matching funds were used exclusively to help support this equipment purchase. This equipment can be used by SCI researchers that are examining the efficacy of various therapeutic interventions to yield changes in protein biomarkers that could subsequently serve as targets for enhancing therapeutic strategies to further facilitate functional recovery.

17. Syracuse University

Materials and resources purchased through this funding have generated essential components and preliminary data for a full proposal to analyze created mutants in more detail and establish a fully-characterized Gene Regulatory Network for the specification of spinal commissural interneurons ventral glutamatergic (CIN V0v) neurotransmitter properties. In the meantime, this funding is enabling personnel to continue to their work and create additional reagents and data. It is also helping researchers to develop and maintain essential mutant lines that will be important for other SCI research.

18. The Feinstein Institute for Medical Research

Funding supported personnel and supplied resources for multiple research projects listed below that aim to improve the understanding of physical recovery and wellness in persons with SCI:

- “Biomarkers of Spontaneous Recovery from Traumatic SCI,” aims to build an easy-to-use, predictive model of recovery after SCI that uses inflammatory mediators. Researchers are studying white blood cells and other biological responses in the blood, as well as recovery of physical abilities, during the first year after SCI.
- “Biomarkers in Pediatric SCI/Abnormalities,” aims to investigate biological responses in discarded blood samples from children with SCI or congenital abnormalities.
- “Strive for Wellness Research Outcomes,” aims to investigate changes in physical and mental wellness as a result of participating in a structured and safe physical activity and wellness program for persons with SCI.

Relatively little is known about the biological processes that influence physical recovery and wellness in people after SCI. The data that researchers will collect will enable them to fill gaps in knowledge and advance the ability to predict and promote physical recovery and overall health in persons with SCI. The data generated by these projects will be used to provide support of feasibility and scientific rationale for larger grant applications in SCI research.

19. University of Rochester

Funding supported personnel and research of multiple projects listed below that aim to generate new data to advance SCI research:

- Genomics and proteomics analyses in spinal cord and skeletal muscle treated by astrocyte transplantation and in attempts to prevent muscle atrophy following SCI.
- Astrocyte populations of different types have been generated using induced pluripotent stem cells (iPSC) technologies and have been transplanted with promising results. The potentially interesting finding has emerged that the most effective astrocytes are predicted to be more effective at managing oxidative stress, a critical astrocyte function that has not previously been studied in respect to use of these cells in SCI repair.
- Rescue of skeletal muscle atrophy and whether it is possible to decrease muscle atrophy following SCI.
- Role of glymphatic system in SCI and its important clinical implications.
- Nitric oxide production and changes that occur after SCI.

20. Winifred Masterson Burke Medical Research Institute

Funding supported personnel, the development of human studies and clinical trials in SCI patients, and the purchase of the following equipment which has been installed and certified for use:

- A butterfly coil for transcranial magnetic stimulation is being used for the “non-invasive paired stimulation to improve lower extremity motor recovery in a chronic SCI” trial which is ongoing.
- An InMotion Anklebot for a correlational study looking to determine if it is a feasible tool in assessing ankle kinematics and spasticity in SCI patients.

A citation for a journal article that has been accepted as a result of this funding is listed below:

Cortes, M., Medeiros, A.H., Gandhi, A., Lee, P., Krebs, H.I., Thickbroom, G., & Edwards, D. (2017). Improved Grasp Function with Transcranial Direct Current Stimulation in Chronic Spinal Cord Injury. *NeuroRehabilitation*, 41(1):51-59. doi: 10.3233/NRE-171456.

TRP in Spinal Cord Injury (Round 1)

Contract Term 8/15/16-8/14/21

**Progress Reporting Period
2/1/17-8/14/17**

2 Awards, Procurement Total: \$8,771,302

1. Columbia University

Sunil K. Agrawal, Ph.D.

\$5,033,354

Project Title: Tethered Pelvic Assist Device (TPAD) and Epidural Stimulation for Recovery of Standing in SCI

Introduction/Background: The goal of this reporting period was to extend the design of TPAD for stand training of patients with SCI. This robotic system mimics the manual training of standing for patients with SCI. The Robotics and Rehabilitation (ROAR) Laboratory at Columbia University is collaborating with the Department of Neurological Surgery at the University of Louisville (UOL).

Progress Towards Specific Aims: The regular exchange of scientific results between the two research teams and extensive discussions about the physical therapy during epidural stimulation and treatment of SCI patients helped better understand present practices. Six (6) members of the ROAR Laboratory observed several stand training sessions at UOL, where they established performance requirements to develop a robotic device based on the architecture of the TPAD system for stand training of SCI patients. Three (3) patients were observed in different phases of their training sessions, with different therapeutic tasks. The ROAR team received feedback from the patients and summarized the requirements of the design. The teams have finalized a simple but effective robotic system design, with all required capabilities and adequate safety measures to support and train SCI patients during standing. This includes both partial weight support and emergency management of the patient if needed. In addition, the system requires easy access and entry of medical professionals to physically interact with the SCI patient during training.

A computer aided design (CAD) model was created that showcases the design, dimensions, and functionality of the system. The detailed parts list of the mechanical, electrical, computers, sensors and other required components were made when the design was finalized.

Future Directions: The detailed parts list have been ordered and components for two (2) devices will be assembled and tested, first at the ROAR Laboratory and then at UOL. The system will be tested first with healthy subjects to evaluate its capabilities and will be integrated within the training of SCI patients.

Impact: The goal of this robotic system is to allow effective assistance, positioning, and support for the SCI patient during training. It will significantly help in the stand training of SCI patients by supporting them at the trunk, pelvis, and the knees.

Citations that have been accepted as a result of this funding are listed below:

Kang, J., Martelli, D., Vashista, V., Kim, H., and Agrawal, S. K. (2017). Robot-Driven Downward Pelvic Pull to Improve Crouch Gait in Children with Cerebral Palsy, *Science Robotics*, 2(8, 2634): 1-12. doi: <https://doi.org/10.1126/scirobotics.aan2634>

Khan, M. I., Prado, A., and Agrawal, S. K. (2017). Effects of Virtual Reality Training with Trunk Support Trainer (TruST) on Postural Kinematics, *IEEE Robotics and Automation Letters*, 2(4), 1. doi: 10.1109/LRA.2017.2724758.

Khan, M. I., Santamaria, V., Kang, J., Bradley, B. M., Dutkowsky, J. P., Gordon, A. M., and Agrawal, S. K. (2017). Enhancing Seated Stability Using Trunk Support Trainer (TruST), *IEEE Robotics and Automation Letters*, 2(3):1609-1616. doi: 10.1109/LRA.2017.2678600

Stegall, P., Zanotto, D., and Agrawal, S. K. (2017). Variable Damping Force Tunnel for Gait Training Using ALEX III, *IEEE Robotics and Automation Letters*, 2(3),1495-1501. doi: 10.1109/LRA.2017.2671374.

2. Research Foundation of CUNY, City College of New York/CUNY School of Medicine

John Martin, Ph.D.

\$3,737,948

Project Title: Combined Motor Cortex and Spinal Cord Stimulation to Promote Arm and Hand Function After Chronic Cervical Spinal Cord Injury

Introduction/Background: The overall goal of this project is to translate a promising therapy for improving arm and hand function after cervical SCI from animal models to humans. Regaining hand function is the highest priority for people with cervical SCI. Researchers use combined brain and spinal cord electrical stimulation to promote recovery, strengthen connections and improve arm and hand function after SCI.

Progress Towards Specific Aims: There has been effective rat replication experiments from the Martin Laboratory to the Carmel Laboratory at Winifred Masterson Burke Medical Research Institute. Emerging data from the Carmel Laboratory suggest efficacy of dual spinal-motor cortex electrical stimulation in improving forepaw manipulation skills and skilled locomotion after fourth cervical segment bilateral contusion, assessed using the Irvine, Beattie, and Bresnahan (IBB) Forelimb Recovery Scale and ladder walking tasks. Preparation for the human phase of the study is ongoing through consultation with other facets of the program and related neurostimulation experiments led by Noam Harel, M.D., Ph.D., at the Bronx Veterans Medical Research Foundation, James J. Peters VA Medical Center.

Future Directions: Researchers will continue to add rats to complete replication studies and for the larger animals they will plan computer modeling studies to optimize the neuromodulation therapy and the fourth cervical vertebra (C4) contusion. They also plan to implement magnetic resonance (MR) imaging before and after injury to improve the lesion outcome. Based on further developments of the ongoing animal experiments, Dr. Harel will pursue IRB approval prior to the fourth year.

Impact: As the phases and aims progress, researchers will move closer to the final goal of being in the position to initiate a trial in humans with cervical SCI.

A citation that has been accepted as a result of this funding is listed below:
Brandenburg, J., Williams, P.T.J.A., Truong, D.Q., Seifert, A., Sarka, A., Xu, J., Bikson M., and Martin, J.H. (2017). *Augmenting Corticospinal Output with Intermittent Theta Burst Stimulation (iTBS) Alone or Combined Trans-Spinal Direct Current Stimulation (tsDC) in a Large Animal Model*. Abstract presented at the Spinal Cord Injury, Society for Neuroscience Meeting, Washington D.C.

Individual Predoctoral/Postdoctoral Fellowships (Round 1)

Contract Term 3/1/16-2/28/19

Progress Reporting Period
3/1/17-8/31/17

5 Awards, Procurement Total: \$695,041

1. Rensselaer Polytechnic Institute

Ryan Gilbert, Ph.D., Christopher Johnson, D.L., B.S.

Predoc: \$135,600

Project Title: Magnetic Alignment of Electrospun Fibers for Treatment of Acute Spinal Cord Contusive Injury

Introduction/Background: Traumatic SCI usually results in an irregularly shaped contusion in the spinal cord that regenerating neurons cannot bridge. Electrospun fiber scaffolds have been successful as bridges that aid in regeneration by guiding neurons and glial cells across the injury. But these scaffolds must be implanted using invasive surgical techniques that risk infection and cause further damage to the tissue from the implantation. Instead, researchers propose using a composite material that consists of magnetic electrospun fibers suspended in an injectable hydrogel. The scaffold would be injected into the injury site, then the fibers would be magnetically realigned in the injury cavity using a magnetic field. This scaffold would be an injectable scaffold that provides aligned topography to guide cells across the injury site. The first step of this project is to optimize the magnetic fibers.

Progress Towards Specific Aims: Expansion of the magnetic nanoparticle (SPION) content in the fibers from 2% up to 8% will provide more options when determining the optimal fibers for realigning in a hydrogel and guiding cells across the injury site. It has been determined that magnetic properties of the fibers were directly related to the SPION content in the fibers. Testing has been conducted to prove whether the length of the fibers affected the movement and there appeared to be no clear trend. Further testing will correlate the hydrogel viscosity, another variable that affects the alignment of the fibers, to the rate of realignment of the fibers. A method to insert the scaffold into a small gauge needle has been developed, delivery of the fibers and hydrogel to a model injury site using the needle and realigning the fibers with two permanent magnets has been demonstrated.

Future Directions: Testing the 3D samples in vitro to determine how primary cells respond to the whole composite system in 3D will be conducted.

Impact: This work would create injectable electrospun fibers that can be reoriented using a magnetic field. Success of this approach would allow electrospun fibers to be delivered using minimally invasive surgical techniques.

A citation that has been accepted as a result of this funding is listed below:

Johnson, C., Gangulay, D., McCarthy, S., Dutz, S., Gilbert, R. (April 2017). *Magnetic Alignment of Electrospun Poly-L lactic acid Fibers for Directed Cell Guidance after Spinal Cord Injury*. Presented at the Society for Biomaterials Conference, Minneapolis, M.N.

2. Research Foundation for SUNY, University at Albany

Ben Szaro, Ph.D., Rupa Choudhary, M.S.

Predoc: \$85,585

Project Title: Intracellular Modulations of Cytokine Signaling Leading to Successful CNS Axon Regeneration in a Vertebrate Model

Introduction/Background: Studying animals such as frogs, which successfully recover from traumatic injury to the CNS can guide design of combinatorial therapies for treating human SCI. In mammals, expression of the SOCS3 gene directly inhibits CNS axon regeneration, but frogs, which also express SOCS3, somehow overcome this inhibition. Another SOCS gene expressed in mammals and frogs, SOCS2, functionally antagonizes SOCS3 in mammalian neural development and tumorigenesis. The hypothesis is that increased SOCS2 expression after injury in amphibians promotes CNS axon regeneration by counterbalancing SOCS3's inhibitory actions. The researchers are testing this hypothesis by comparing SOCS2 (Aim 1) and SOCS3 (Aim 2) expression when animals recover from CNS injury (e.g., frog optic nerve and tadpole SCI) with when they do not (frog SCI) and by testing effects of manipulating expression of these genes on recovery (Aim 1, SOCS2; Aim 2, SOCS3).

Progress Toward Specific Aims: In previous reporting periods, the trainee developed reagents and refined techniques for measuring expression of SOCS2 and SOCS3 proteins and mRNAs and made reagents for inhibiting their expression in regenerating and developing CNS neurons. In the current reporting period, she conducted further qRT-PCR experiments and added RNA-seq data to quantify changes in expression of SOCS2 and SOCS3 mRNA during optic nerve regeneration. She also collected further data using in situ hybridization and immunohistochemistry on changes in SOCS2 and SOCS3 mRNA expression in the retina during optic nerve regeneration, conducted additional experiments to validate the specificity of the antibodies she generated against *Xenopus* SOCS2 and SOCS3, and carried out further polysome profiling experiments, which collectively indicated that disparities between expression of the SOCS3 mRNA vs protein were not due to differences in the translational efficiencies of the mRNAs with injury. She also continued testing her antisense morpholino oligonucleotides to determine which ones can best be used to manipulate expression of SOCS2 and SOCS3.

The fellow presented her results at a local symposium highlighting research being done in the Life Sciences at SUNY-Albany, and to the Department of Biological Sciences, as well as to her dissertation committee. In addition, she presented a poster at the Northeast Regional Meeting for the Society for Developmental Biology. The committee helped her formulate plans for her future and ongoing studies. The fellow also plans to attend the national meeting of the Society for Neuroscience and to prepare her first publication on her work.

Future Directions: After finishing her expression studies of optic nerve injury, the fellow will expand her studies to include tadpole and frog SCI, and begin manipulating SOCS2 and SOCS3 expression in CNS injury and development. She is also planning experiments to determine whether the discrepancy between SOCS3 mRNA expression, which increases with injury, and protein expression, which does not, is due to increased turnover of SOCS3 protein.

Impact: The project will provide new information about how a cell signaling pathway that inhibits CNS axon regeneration in mammals is overcome in an organism that recovers naturally. This knowledge should provide key insights into how recovery can be promoted in human SCI. The project also provides support for training a Ph.D. student in preparation for a career in research and teaching in regenerative medicine.

3. The Research Foundation of CUNY obo City College of New York

John Martin, Ph.D., Alzahraa Amer, M.S.

Predoc: \$135,600

Project Title: Modulating Spinal Cord Neural Activity to Promote Recovery of Motor Function After SCI

Introduction/Background: SCI interrupts the corticospinal tract (CST), which connects the motor cortex, where movements are initiated with the spinal cord and where movements are more directly controlled by the actions of spinal cord neurons on muscle. The overall aim of this project is to strengthen the connections of the CST using spinal cathodal direct current electrical stimulation to promote motor function after injury. Direct current electrical stimulation is a non-invasive way to modulate spinal cord neuronal activity.

Progress Toward Specific Aims: For Aim 1, researchers showed that spinal activation by direct current (DC) stimulation alone enhanced CST outgrowth. For Aim 2, researchers have completed the cervical SCI study using combined spinal DC stimulation to enhance spinal cord function and brain stimulation to augment CST axonal outgrowth. The predoctoral student examined the role of spinal DC stimulation in strengthening CST connection strength after cervical spinal injury. She found that spinal DC stimulation strongly promotes the capacity of M1 stimulation to evoke muscle responses after injury. This improved the efficacy of the brain stimulation part of therapy. In that study, researchers observed a significant amount of CST axon sprouting and improvement in motor performance compared with injured animals that did not receive stimulation.

Future Directions: The hypothesis is that after cervical SCI, spinal motor circuits are poorly excited by motor cortex stimulation and that spinal DC stimulation is a way to enhance the efficacy of motor cortex stimulation. Researchers found that by increasing spinal excitability during motor cortex stimulation with DC stimulation, they can make the motor cortex stimulation much more effective in activating spinal motor circuits.

Impact: Spinal cord DC stimulation has the potential to become an important non-invasive neuromodulatory tool to promote spinal motor function after injury and to enhance the therapeutic effects of brain stimulation.

A citation for a journal article that has been accepted as a result of the funding is listed below:

Zareen, N., Shinozaki, M., Ryan, D., Alexander, H., Amer, A., Truong, D. Q., ... & Martin, J. H. (2017). Motor Cortex and Spinal Cord Neuromodulation Promote Corticospinal Tract Axonal Outgrowth and Motor Recovery after Cervical Contusion Spinal Cord Injury. *Experimental Neurology*, 297: 179-189. doi: 10.1016/j.expneurol.2017.08.004.

4. Winifred Masterson Burke Medical Research Institute

Jason Carmel, M.D., Ph.D., Hongguen Park, Ph.D.

Postdoc: \$172,902

Project Title: Dissecting and Strengthening Corticospinal Connections After Spinal Cord Injury Using Advanced Neuroscience Methods

Introduction/Background: Spinal cord injury is a devastating disease that causes paralysis by disconnecting the brain and spinal cord. While motor function is impaired, some connections are spared and provide a potential substrate for therapeutic treatment. In this study, researchers aimed to identify the connections responsible for spontaneous recovery and to strengthen them to improve recovery.

Progress Toward Specific Aims: Their goal is to identify and strengthen the connections between brain and spinal cord that are responsible for spontaneous recovery of hand movement after cervical spinal cord injury. To identify these connections, researchers trace the connections with fluorescent proteins delivered by virus. To prove the necessity of these connections in functional recovery, they inactivate them using a technique that blocks electrical signals in specific connections.

To improve tracing efficiency, researchers are adopting new viruses that deliver brighter fluorescent proteins faster. They compared the tracing efficacy of new viruses to old ones and were preparing the viruses. The inactivation system is under optimization to inactivate candidate connections without inducing damage to the spinal cord by testing various conditions.

Future Directions: In the next period, researchers will try to identify the candidate connections that are responsible for spontaneous recovery after spinal cord injury by using the new viral tracers. They will test if the optimized injection condition of the inactivation viruses is appropriate to silence intact connections without damage to the spinal cord.

Impact: Once this project is completed successfully, the results will provide the information regarding where in the brain and spinal cord to stimulate with electrical current to improve motor recovery.

5. Winifred Masterson Burke Medical Research Institute

Jian Zhong, Ph.D., Mariel Voutounou, Ph.D.

Postdoc: \$165,354

Project Title: Promoting Intrinsic Growth Competency of Injured Neurons Using Genetic and Small Molecule Approaches

Introduction/Background: Neural repair after SCI remains challenging due to the limited intrinsic regenerative capacity of mature CNS. In addition, the inhibitory environment in CNS (growth inhibitory molecules such as Nogo, MAG, OMgp) poses another barrier to axon regeneration after injury. Recently, researchers have reported that re-activation of specific intraneuronal growth signaling B-RAF is sufficient to promote axon growth and regeneration. They will investigate the synergic effects of B-RAF activation and the elimination of growth inhibitory molecules on axon regeneration in SCI models. Another goal of this study is to identify “druggable” B-RAF downstream effectors as potential targets to promote axon growth.

Progress Toward Specific Aims: Researchers have completed all the trainings for the study, including all surgical procedures, post-operative care, drug administration, etc. They have compared two well-characterized mouse lines expressing Cre deleter in cortical layers V/VI and in the forebrain to determine the best model for the study. They are in the process of breeding B-RAF gain of function (GOF) mice and myelin-based inhibitor Nogo, MAG, OMgp triple knock out mice. They have designed and generated viral constructs to up- and down- regulate downstream effectors of B-RAF signaling pathway identified via RNAseq.

Future Directions: Investigate the effects B-RAF GOF in the presence or absence of myelin-based inhibitor on axon regrowth in CNS injury models. Use viral constructs to test their ability to promote axon regeneration after SCI.

Impact: Researchers aim to boost the regenerative effect of B-RAF activation on injured mature CNS axons by modulating its downstream effectors or knocking out growth-inhibitory cues. The findings of this study will contribute towards a better understanding of the intrinsic signaling mechanisms of axon regeneration and the development of therapeutic strategies.

CART/IDEA

IDEA Contract Term 11/1/15-10/31/17; CART Contract Term 11/1/15-10/31/18

Progress Reporting Period

11/1/16-4/30/17

9 Awards, Procurement Total: \$5,719,548

1. **Albert Einstein College of Medicine**

Principal Investigator: David Sharp, Ph.D.

CART: \$1,197,182

Project Title: Harnessing Microtubules to Enhance Urological Function after Spinal Cord Injury

Introduction/Background: SCI-related research both in animals and humans has traditionally focused on repairing, protecting or regenerating motor tracts, while changes in the sensory and autonomic nervous system after SCI remain understudied.

Progress Toward Specific Aims: This research evaluates the recovery of function in a rat model of SCI following Fidgetin-like 2 (FL2) knockdown. They are now using a rat myofibroblast cell line generated in their laboratories to screen siRNA delivery reagents to optimize dosages before in vivo administration. In addition, they are also using laser light scanning to analyze size of the different nanoparticle formulations and to determine the extent to which low levels of sonication of nanoparticle suspensions facilitates dispersion/disaggregation of the particles to increase their in vivo penetration through the dura.

The research also focuses on determining the mechanism by which FL2 promotes functional recovery after SCI. Their research suggests that FL2 localization in the axon is dependent on the microtubule cytoskeleton, but that in certain locations like the growth cone, this localization is less microtubule dependent. It is possible that the protein is anchored and/or more protected from degradation at certain sites where it's functioning is especially critical, like the growth cone.

Future Directions: Researchers will now focus their efforts on implementing the use of the nanoparticles and perform dose-response studies with SCI rats to optimize the treatment dosage-range and correlate levels of FL2 silencing with those of recovery of locomotor and urogenital functions.

They will also conduct a series of in vitro experiments aimed at better understanding the role of FL2 in regulating growth cone steering. Preliminary data indicates that depletion of FL2 from neurons attenuates the effects of inhibitory substrates on axon growth and guidance. They will confirm these promising findings and look more closely at changes in microtubule dynamics as growth cones interact with inhibitory substrates.

Impact: This study identifies a novel therapeutic target for promoting axon regeneration and recovery of SCI-related loss of motor and urogenital functions; will advance research in underexplored areas of autonomic and sensory dysfunction following SCI;

and will advance our understanding of how the microtubule cytoskeleton can be targeted to promote neural regeneration in the central nervous system.

2. Burke Medical Research Institute

Principal Investigator: Dianna Willis, Ph.D.

IDEA: \$448,978

Project Title: Alterations in Extracellular Vesicle Communication as a Cause of NMJ Dysfunction after SCI

Introduction/Background: Following spinal cord injury (SCI), changes occur that have been implicated in driving secondary events after the initial, primary injury. Among these changes are alterations in the neuromuscular junctions (NMJs) at sites distant from the injury. The working hypothesis is that changes in signals from the muscle cells to the neuron at the NMJ are a cause of NMJ dysfunction.

Progress Toward Specific Aims: The goal of Aim 1 is to identify the muscle-secreted microRNA changes following SCI. Researchers have generated the SCI animals, collected tissue from these animals, and isolated exosome preparations which were tested for the presence of microRNAs, and performed RNA deep sequencing on these preparations. Samples have been collected for electron microscopy, and the antibodies required for the immuno-EM have been optimized. These experiments are ongoing. Aim 2 is designed to elucidate the role of mir206 in the maintenance of NMJs. Tagged-mir206 constructs have been used to confirm the transfer from muscle cells to axons, and NMJ morphological analyses with knockdown and overexpression have been performed. The goal of Aim 3 is to determine whether muscle-secreted microRNAs regulate local protein synthesis to facilitate NMJ maintenance. Researchers have completed the bioinformatics-based target identification for this aim and have begun these experiments.

Future Directions: Deep sequencing has been completed, providing a global picture for how the muscle to neuron communication is altered following injury. Researchers are now focusing on the functional impact of these alterations.

Impact: Researchers believe that a better understanding of the fundamental means of communicating between cells, and how this communication is disrupted following SCI, will point to potential therapeutic strategies for maintaining the NMJ following injury. Strategies that limit the propagation of secondary damage following injury would greatly impact long term recovery and quality of life.

3. Burke Medical Research Institute

Principal Investigator: Jason Carmel, M.D., Ph.D.

IDEA: \$450,419

Project Title: Delayed Versus Immediate Motor Training Following Brain Stimulation to Enhance Recovery in Rats with Chronic Corticospinal Tract Injury

Introduction/Background: For people with cervical spinal cord injury (SCI), restoring arm and hand function is the top priority. Researchers want to understand how to combine hand therapy (exercise) and electrical brain stimulation in chronic SCI. They hypothesize that training will be most effective delivered two weeks after electrical stimulation.

Progress Toward Specific Aims: To promote functional recovery after injury, researchers must create a motor task that is sensitive to injury as well as easy to learn. The task requires rats to

turn a knob and tests supination, the ability to rotate the hand from palm down to palm up, which is critical to dexterity. A previous iteration of the task was highly sensitive to injury, but required a long training period. Researchers decreased the training time by adjusting the protocol. They also increased the difficulty, which allows us to show deficits in rats, even though rats rely less on the spinal connection that they have to cut. Researchers have demonstrated that improvement in motor skill with brain stimulation is associated with sprouting of brain-to-spinal cord connections. To understand how training and stimulation alters these connections they have successfully combined nerve cell tracers so they can inject the brain and measure nerve fibers in the spinal cord and, in the same animal, inject the spinal cord and determine the brain cells that innervate the spinal cord.

Future Directions: Next steps include comparing behavioral differences in those rats that received immediate versus delayed rehabilitation after chronic impairment and quantifying labeled CST axons and neurons in those same animals.

Impact: Understanding the proper timing of training after stimulation can help optimize this combination, which can be quickly applied to people with SCI.

4. CUNY City College of New York

Principal Investigator: John Martin, Ph.D.

CART: \$990,000

Project Title: Repairing the Damaged Corticospinal Tract after Cervical Spinal Cord Injury

Introduction/Background: The scope of the project is to develop electrical-stimulation based therapies for SCI. Researchers use a rat model of contusion injury of the upper part of the spinal cord, termed the cervical spinal cord. Their approach to therapy is to electrically stimulate the motor cortex, where movements are initiated, and also stimulate the spinal cord, where movements are executed, to promote connections of the corticospinal motor system after injury. In the prior reporting period, they completed development of their SCI model. In the present reporting period, they implemented their initial motor cortex-spinal cord stimulation plan.

Progress Toward Specific Aims: Researchers completed comparison of two (2) animal groups in the first set of Aim 1 experiments: injury only and injury plus motor cortex and spinal cord stimulation and have presented these findings at the Society for Neuroscience Annual Meeting (2016). Compared with animals that were only injured, which showed no behavioral improvements, the injury plus stimulation group showed significant improvement in skilled walking and forepaw manipulation. These behavioral improvements were accompanied by enhanced connections between the motor cortex and parts of the spinal cord below the lesion, in the stimulated compared with the non-stimulated group.

Researchers also examined the effect of trans-spinal direct current stimulation (tsDCS) on the spinal actions of motor and peripheral sensory fibers. They found significant, albeit minimal, suppression of the sensory fiber response by anodal stimulation and little or no effect of cathodal tsDCS. By contrast, they found strong significant facilitation of the motor response by cathodal stimulation and minimal suppression by anodal stimulation.

The overall conclusion is that cathodal stimulation facilitates corticospinal system function whereas anodal stimulation weakly suppresses sensory function.

Future Directions and Impact: During the next period, researchers plan to complete the first contusion injury study and further pursue study of the interactions of sensory fibers and the corticospinal system. They also plan to begin modeling of the contusion injury to optimize spinal electrode development. If successful, the impact of their studies will include establishment of a minimally-invasive spinal neuromodulatory therapy for humans that targets the corticospinal system.

5. Health Research, Incorporated

Principal Investigator: Jonathan Carp, Ph.D.

IDEA: \$442,373

Project Title: Role of Abnormal Urethral Sphincter Motoneuron Properties in Urinary Tract Dysfunction after Spinal Cord Injury

Introduction/Background: This project addresses how spinal cord injury (SCI) affects the nerve cells that control the external urethral sphincter (EUS), a muscle crucial for controlling urinary function. The central hypotheses are that: SCI produces long-lasting changes in these nerve cells; and these changes cause inappropriate EUS muscle activation, thereby impairing urinary control. The first Specific Aim is to identify SCI-induced abnormalities in these nerve cells by directly measuring EUS nerve cell properties with microelectrodes using SCI or intact rats. After collecting control data, the drug sensitivity of these nerve cells will be assessed to determine the mechanism of these effects. The second Specific Aim is to determine whether SCI-induced changes in EUS nerve cell properties identified in the first Specific Aim will contribute to SCI-induced urinary dysfunction by assessing voiding capabilities of rats with or without SCI before and during spinal administration of the same drugs used in the first Specific Aim.

Progress Toward Specific Aims: The new laboratory was brought into compliance with animal facility standards for accreditation for the first Specific Aim. They also completed configuration of recording systems, and hired and trained an Assistant Research Scientist to assist with the spinal slice procedure, and data acquisition and analysis.

For the second Specific Aim, researchers performed spinal injuries in rats for use in drug evaluation experiments, which are currently in progress. They also continued development and validation of method for performing cystometry in awake, freely-moving rats. A manuscript has been submitted to the Journal of Neurotrauma.

Future Directions: By relocating and staffing their laboratory, refining their experimental design, and beginning experiments, researchers are now well-positioned to achieve the Aims of the award.

Impact: Abnormal EUS activity after SCI can make voiding difficult or impossible without catheterization. The progress achieved here will facilitate evaluation of drugs for treating this problem.

6. Icahn School of Medicine at Mount Sinai

Principal Investigator: Hongyan Zou, M.D., Ph.D.

IDEA: \$360,000

Project Title: The Role of HDAC3 in the Epigenetic Regulation of Functional Polarization of Microglia and Macrophages after Spinal Cord Injury

Introduction/Background: Spinal cord injury (SCI) results in neurological deficits that seldom recover. SCI triggers a multiphasic immune response. The innate immunity consists of microglia, resident immune cells in the central nervous system, and blood-born monocytes that differentiate into macrophages at the injury site. The innate immune response plays a dual role for tissue repair after SCI. Developing new strategies that can maximize the pro-repair while minimizing the detrimental aspect of the immune response represents a promising new direction for SCI therapy. In order to realize the promise of immunomodulatory therapy, a deeper understanding of the regulatory mechanisms of the diverse functions of microglia and macrophages in SCI is imperative. This proposal studies the novel function of HDAC3 in mediating the innate immune response after SCI. HDAC3 is an epigenetic enzyme that modifies the histone acetylation status of target genes. Researchers are focusing on studying the potential therapeutic effect of a specific HDAC3 inhibitor in promoting functional recovery after SCI.

Progress Toward Specific Aims: Researchers have conducted a time course study to further characterize the expression dynamics of HDAC3 after SCI. They have expanded their in vivo study in SCI models to further confirm a neuroprotective phenotype and improved functional recovery using a specific HDAC3 inhibitor in SCI model. Finally, for mechanistic understanding, they demonstrated a dampening of cytokines at the injury milieu and downregulation of inflammatory genes in the innate immune cells with HDAC3 inhibition.

Future Directions: Researchers will deepen their mechanistic understanding of the role of HDAC3 in mediating the innate immune response after SCI. Specifically, they will investigate the HDAC3-regulated gene network in microglia and macrophages in SCI.

Impact: The study will validate HDAC3 as a critical epigenomic regulator that integrates injury signals to calibrate the innate immune response after SCI. The study promises to establish a novel approach of immunomodulation for SCI.

7. Icahn School of Medicine at Mount Sinai

Principal Investigator: Noam Harel, M.D., Ph.D.

IDEA: \$391,353

Augmenting Hand Muscle Control in Cervical SCI through Paired Cortical and Cervical Stimulation

Introduction: Researchers aim to improve function of spared nerve circuits after spinal cord injury (SCI) through the use of electrical and magnetic stimulation.

They have developed a form of non-invasive electrical stimulation over the spinal cord that activates muscles in both hands simultaneously and comfortably. This technique, called cervical electrical stimulation (CES), works at the skin surface – no surgery is required. In this proposal, they are investigating the basic mechanisms, safety, and short-term efficacy of this new technique.

Progress Toward Specific Aims: To date, 11 subjects without SCI and four (4) subjects with SCI have undergone CES testing. No serious adverse events have occurred. Two (2) subjects had minor skin irritation at the site of stimulation.

Researchers have preliminarily confirmed that a specific electrode configuration achieves the most robust results. At low intensities, CES activates sensory nerve roots that enter the spinal cord. At higher intensities in some but not all subjects, CES activates motor nerve roots that have already left the spinal cord.

When pairing CES with magnetic stimulation of the brain, they have observed an increase in nerve transmission between the brain and hand muscles either immediately after single pairs of stimulation, or for up to 30 minutes after a 20-minute period of stimulation.

Future Directions: Researchers will continue testing both Aims – in a total of 12 subjects with and 12 subjects without SCI.

Impact: This approach to stimulation has the potential to strengthen the brain's control over the spinal cord after SCI. It could also synergize with other types of treatment, such as physical rehabilitation and future drug treatments.

Citations for publications and meeting abstracts that have been accepted as a result of the funding are listed below:

Harel, N. Y., & Carmel, J. B. (2016). Paired stimulation to promote lasting augmentation of corticospinal circuits. *Neural Plasticity*, 7043767. doi: <http://dx.doi.org/10.1155/2016/7043767>.

Harel, N. Y., Yung, L., Romero, A. F., Santiago, T. M., Guber, K. S., Kastuar, S., . . . Bauman, W. A. (May, 2016). *Cervical transcutaneous stimulation to increase cortical transmission to hand muscles*. Abstract presented at the 9th World Congress for Neurorehabilitation, Philadelphia, Pennsylvania.

8. Regenerative Research Foundation

Principal Investigator: Sally Temple, Ph.D.

CART: \$1,097,684

Project Title: Sustained Delivery of IL10 and SHH to Promote Spinal Cord Regeneration After Injury

Introduction/Background: Spinal cord injury 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. Researchers have developed bioengineered micro-sized beads made of a biodegradable, biocompatible and FDA approved material. They propose to test whether a combination of sustained IL10 plasmid (IL10 pDNA) and sustained sonic hedgehog growth factor (SHH) delivered via biodegradable biocompatible microbeads to the injury site will counteract inflammatory processes, promote a regenerative environment and improve recovery after spinal cord injury.

Progress Toward Specific Aims: During this period researchers have generated both SHH and IL10 pDNA microbeads and demonstrated their activity in vitro. In addition,

researchers have completed the animal experiments for Aim 1B “Analysis and characterization of in vivo expression of IL10 pDNA and SHH, and the cytokine and macrophage profile after microbead delivery into acute and chronic SCI rat models”. All assays have been completed and the statistical data analysis is in progress.

Future Directions: In the upcoming year they plan to study the effect of IL10 pDNA microbead delivery on functional locomotor and histological recovery in acute and chronic SCI. Researchers will transplant IL10 pDNA-releasing microbeads into acute and chronic rat contusion SCI models. The efficacy of the treatment will be assessed by monitoring functional recovery with motor and sensory tests. The effect of IL10 pDNA microbead administration will be analyzed using histological and molecular analysis.

Impact: This project will add to the research team's overall understanding of the role of IL-10 pDNA and SHH in altering the post-injury inflammatory processes in the spinal cord, and their potential therapeutic effectiveness for the treatment of spinal cord injury. They will also obtain data on the effectiveness of combinatorial treatment with IL-10 pDNA and SHH for recovery from SCI.

9. SUNY Downstate Medical Center

Principal Investigator: Joseph Francis, Ph.D.

IDEA: \$341,559

Project Title: 24/7 Use of Fully Integrated Bi-Directional Autonomous Brain Machine Interface in Non-Human-Primates

Introduction/Background: Over the past decade, it has been clear that the research team can record neural activity from the brain and allow individuals the ability to control computer cursors and other such devices. The current work aims to allow users control over an anthropomorphic robotic arm, or simulation of such arm, throughout the course of the day. In addition, researchers will be giving sensory feedback through brain stimulation with a goal to determine how such a system becomes incorporated with the users over time.

Progress Toward Specific Aims: All appropriate equipment has been purchased and researchers are now setting up the full BMI system to work with the wireless recording and the wireless recording/stimulation systems. They will be integrating systems from Blackrock Microsystems as well as Triangle Bio-systems. Once the implant design is finished, the first animal will be implanted.

Future Directions: Over the remainder of the project, they will start to test how continuous use of such a system changes the neural dynamics, the user's performance and neural plasticity.

Impact: The impact of this work should allow us to determine if researchers can allow a user to control a BMI for movement while giving artificial sensory input without causing neuropathic pain. This is a necessary step before such systems are implanted into humans.

A citation for a journal publication that has been accepted as a result of the funding: Choi, J. S., Brockmeier, A. J., McNiel, D. B, Kraus, L. M., Príncipe, J. C., & Francis, J. T. (2016). Eliciting naturalistic cortical responses with a sensory prosthesis via optimized microstimulation. *Journal of Neural Engineering*, (13)5:056007. doi: 10.1088/1741-2560/13/5/056007.

Appendix 3

NEW YORK STATE SPINAL CORD INJURY RESEARCH BOARD

As of December 31, 2017

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