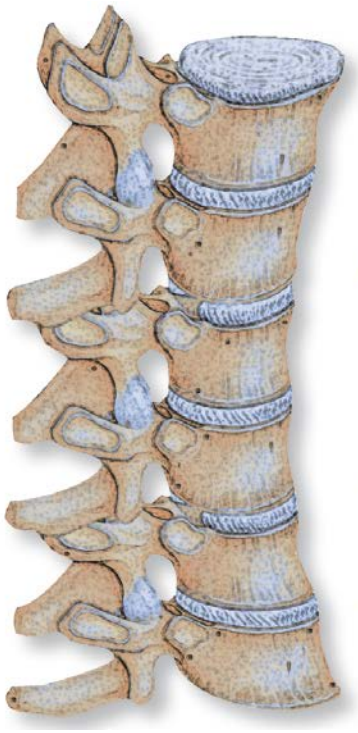
NEW YORK STATE OF OPPORTUNITY. Department of Health



SPINAL CORD INJURY RESEARCH BOARD

Annual Report

January 1, 2016 to December 31, 2016

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 SCIs[1] 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.

The economic costs of SCI are great. 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 $347,896 to more than $1,065,980, with annual costs thereafter ranging from approximately $42,256 to $185,111.[2] 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. It 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. 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, 2016. Web. 5 July 2016. https://www.nscisc.uab.edu/

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 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 2016 (see Section IV. below).

Bylaws

No changes were made to the SCIRB's bylaws in 2016. The bylaws can be found at http://www.wadsworth.org/extramural/spinalcord/advisory-board/statutes-bylaws.

IV. MAJOR ACTIVITIES OF THE SCIRB

At its January 20, 2016 meeting, the SCIRB met and programmed the following funding opportunity and Requests for Applications (RFAs):

- Individual Predoctoral and Postdoctoral Fellowships in Spinal Cord Injury (Round 2) RFA
- Solicitation of Interest for Support of Current Peer-reviewed Spinal Cord Injury Research in New York State (Round 6)
- Translational Research Projects (TRP) in Spinal Cord Injury RFA

At its September 7, 2016 meeting, the SCIRB met and recommended funding for 11 awards from the "Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activities (IDEA)" RFA, for a total of $6.2 million. These are three- and two-year awards respectively. A tabular summary of this procurement can be found in Appendix 1.

In fiscal year (FY) 2016, $8.5 million was programmed to support SCI research.

Previously Recommended SCI Research Contracts

In February 2016, the Institutional Support for Spinal Cord Injury Research (Round 5) 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. Nineteen (19) 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 2016, five Individual Predoctoral and Postdoctoral Fellowships in Spinal Cord Injury Research contracts began. Six awards were recommended for funding, however, one fellow declined due to prior acceptance of National Institutes of Health (NIH) funding. The scientific progress resulting from these three year awards can be found in Appendix 2.

In August 2016, two contracts for the Translational Research Projects in Spinal Cord Injury (Round 1) began. The SCIRB is eager to learn about the progress resulting from these contracts at Columbia University and the Research Foundation of CUNY at the City College of NY, CUNY School of Medicine. Their progress will be featured in the 2017 SCIRB Annual Report.

By the end of 2016, three Collaborations to Accelerate Research Translation (CART) and six IDEA contracts completed their first year. The scientific progress resulting from these three- and two-year awards, respectively, can be found in Appendix 2.

Appendix 1
2016 PART/IDEA Recommendations for Award

Organization	*Principal Investigator*	*Funding Mechanism*	*Project Title*	*Recommended Award*
Bronx Veterans Medical Research Foundation, Peters VA	Hesham Tawfeek, M.D. William Bauman, M.D. Christopher Cardozo, M.D.	IDEA	Role of T cells in Bone Loss After Spinal Cord Injury	$356,999
Cornell University	Chris B. Schaffer, Ph.D.	IDEA	Imaging Neural Activity in the Spinal Cord of Awake Mice After Spinal Cord Injury	$350,876
Research Corporation of Long Island, Inc., Northport VA Sub-applicant: Houston Methodist Research Institute	Victor L. Arvanian, Ph.D., D.Sci Sub-applicant: Philip J. Homer, Ph.D. Hayk Petrosyan, Ph.D.	PART	Neuroplasticity Integrting Human Induced Neuralized Pluripotent Stem Cells (NiPSCs) in SCI Animals	$935,867
Research Foundation for SUNY Stony Brook	Sue Ann Sisto, Ph.D. Victor Arvanian, Ph.D. Hayk Petrosyan, Ph.D. Janice Sniffen, Ph.D.	PART	Effects of Spinal Electromagnetic Stimulation and Locomotor Training on Motor Recovery and Walking in Incomplete SCI	$989,199
Research Foundation for SUNY Stony Brook	Irene C. Solomon, Ph.D. William F. Collins, Ph.D.	IDEA	Therapeutic Potential of Mild to Moderate AIH on LUT and Respiratory Function in SCI	$355,111
Research Foundation for SUNY, University at Albany	Ben G. Szaro, Ph.D.	IDEA	Functional Analysis of Genes Implicated in Successful CNS Axon Regeneration	$359,738

Organization	*Principal Investigator*	*Funding Mechanism*	*Project Title*	*Recommended Award*
The Research Foundation of CUNY obo College of Staten Island	Maria Knikou, P.T., Ph.D.	PART	Transspinal-Transcortical Paired Stimulation for Neuroplasticity and Recovery After SCI	$947,004
The Trustees of Columbia University in the City of New York	Ulrich Hengst, Ph.D.	IDEA	Pumilio 1 and 2 Control Axon Regrowth by Shaping the Axonal Transcriptome	$360,000
Weill Medical College of Cornell University Sub-applicant: Winifred Masterson Burke Medical Research Institute	Anthony Sauve, Ph.D. Sub-applicant: Brett C. Langley, Ph.D. Caitlin Hill, Ph.D.	PART	NAD-Augmenting Agents to Enhance Neural Survival and Function Following Spinal Cord Injury	$890,241
Winifred Masterson Burke Medical Research Institute Sub-applicant: Massachusetts Institute of Technology	Dylan J. Edwards, Ph.D., P.T. Mar Cortes, M.D. Sub-applicant: Hermano I. Krebs, Ph.D.	IDEA	Improving Hand Function in Chronic SCI with Combined Robot Training and Transcranial Direct Current Stimulation	$359,000
Winifred Masterson Burke Medical Research Institute	Jian Zhong, Ph.D. Dylan Edwards, Ph.D.	IDEA	Visualizing New Synapses and Their Activity in the Injured Spinal Cord	$360,000
			Total (11 awards)	**$6,264,035**

Appendix 2

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

Institutional Support for Spinal Cord Injury Research, Round 5

Contract Term 2/1/16 – 8/31/16

Progress Reporting Period 2/1/16 – 8/31/16

19 Awards, Procurement Total: $6,407,142

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

A Thermo Scientific™ HistoStar™ Embedding Workstation was purchased and has been installed and certified for use to serve as a SCI research shared resource and will be listed in future grant applications. The specific projects for which the equipment will be used deal with the trophic properties of dorsal root ganglia in SCI and posttraumatic spinal cord disease. This state-of-the-art embedding station has generated optimally embedded samples of human autopsy tissues (spinal cord and dorsal root ganglia) that were further processed to high-quality tissue sections. Funding was also used to support two Principal Investigators, Dr. Johnathan R. Wolpaw and Dr. Arnulf H. Koeppen, and staff who addressed the objectives of two projects.

Citations for any publications or meeting abstracts that have been accepted and/or submitted as a result of the funding:

Eftekhar, A., Mccane, L. M., Heckman, S. M., Schalk, G., Thompson, A. K., & Wolpaw, J. (November, 2016). *Operant conditioning of spinal reflexes: Development of a user-friendly clinical research system.* Abstract presented at the annual meeting of the Society of Neuroscience, San Diego, California.

Koeppen, A. H., & Becker, A. B. (2016). *Friedreich ataxia: hypoplasia of spinal cord and dorsal root ganglia*. Manuscript in preparation, Albany Research Institute, Inc., Albany Stratton VA Medical Center.

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

Eleven equipment items, (such as a motorized tilt table, digitrapper pH-Z monitors and corresponding catheters, FastPrep24-5 tissue homogenizer, etc.), and several laptops were purchased and have been installed and certified for use to serve as a SCI resource for data collection and investigator use on projects that deal with cardiovascular autonomic, endocrine, gastrointestinal, pulmonary, molecular and exo-skeletal walking projects. Each equipment item was purchased with the intent to enable the investigator to conduct preliminary work to obtain pilot data for their study objective. The findings from conducting these pilot studies will serve as the basis for future funding opportunities. Funding was also used to support staff to integrate the new equipment into the research projects, initiating the study procedures and commencing/continuing data collection. The ultimate expectation is that the findings from these investigations will

identify new information that will lead to improvements in the understanding of the medical consequences of SCI, treatment, and/or rehabilitation strategies that will improve care and quality of life for persons with SCI.

As of this reporting period, there has been no dissemination of findings for any of the inclusive study proposals.

3. Columbia University

A study to evaluate the performance of a novel light-weight wire-driven exoskeletons C-Alex was conducted. Weights were added to the thigh and shank cuffs on the legs; the masses were added to the thigh cuffs to simulate heavier exoskeletons.

Also, a B-Alert X10 Wireless EEG Headset and Fetch robot were ordered, which will be integrated in current and future work with C-Alex.

Citations for publications or meeting abstracts that have been submitted as a result of the funding:

Jin, X., Cai, Y., Prado, A., & Agrawal, S. K. (2017). *Effects of Exoskeleton Weight and Inertia on Human Walking.* Abstract submitted to the Institute of Electrical and Electronics Engineers Association's International Conference on Robotics and Automation, Singapore.

4. Albert Einstein College of Medicine (AECOM)

A CatWalk XT and ETHOVISION XT from Noldus were purchased, as well as an Infinite Horizon Impactor from PSI, and AMAXA 4D Nucleofector from LONZA. This major equipment is fully operational and has been extensively used in ongoing SCI studies. Behavioral and in vitro data obtained using this equipment have shown that the locomotor and urogenital deficits observed in rats following SCI are accompanied by a marked time-dependent increase in FL2 expression at the lesion site, which returns to levels similar to non-injured control levels at 21 days after injury.

Funds were also utilized to purchase and test a novel nanoparticle platform for topical delivery of FL2-siRNA, which is expected to provide easier manipulation and enhanced penetration through the spinal cord dura. By increasing researchers' experiences and the availability of these new tools, AECOM will be able to foster the development of new collaborations and SCI studies.

Funding also supported Principal Investigator, Dr. Sylvia O. Suadicani, and other personnel, and supplies were provided to researchers who are actively participating in SCI studies. Funding provided by this award significantly expanded the SCI research capabilities at AECOM not only in terms of equipment but also development of novel experimental protocols.

Citations for publications or meeting abstracts that have been accepted as a result of the funding:

Baker, L. A., Charaffedine, R., Tar, M. T., Nacharaju, P., Suadicani, S. O., Friedman, J. M., . . . Sharp, D. J. (December, 2016). *Fidgetin-like 2, a novel microtubule regulator,*

can be targeted in vitro and in vivo to enhance axon regeneration. Presented at Microtubule Dynamics, American Society for Cell Biology Annual Meeting, San Francisco, California.

5. Cornell University

Funding supported two distinct projects, one in Dr. Chris B. Schaffer's laboratory and one in Dr. Ronald Harris-Warrick's laboratory.

Dr. Schaffer's laboratory purchased a system that enables them to rapidly move the microscope objective to keep the same imaging plane in focus, to reduce out-of-plane motion artifact due to animal respiration and heartbeat. They also designed and built a limb-tracking system that enables them to quantify limb motion for spine-fixed animals while they are being imaged. They have built a system containing two infrared illuminators and four cameras operating at a frame rate of 200 fps. Combined with the StreamPix7 video tracking software installed, they are able to automatically detect and track the position of front and hind paws, limbs, nose and tail in 3D with high temporal resolution. Ultimately, they are able to delineate a clear correlation between individual neuronal firing patterns imaged with three photon fluorescence with limb movements of the entire animal imaged with this system. The imaging approaches developed and optimized as a result of this funding has contributed to new funding both in Dr. Schaffer's laboratory and in their collaborators laboratories.

Dr. Harris-Warrick's laboratory used this funding for staff support. The researchers work has provided a baseline understanding of changes in intrinsic properties of several neuron classes after SCI, and advanced their work on modulation to include dopamine as well as serotonin.

Citations for publications or meeting abstracts that have been accepted as a result of the funding:

Cheng, Y. T., Bastille, I. M., Cruz-Hernandez, J. C., Ouzounov, D. G., Wang, T., Li, X., Nishimura, N., . . .Schaeffer, C.B. (2016). *In-vivo three-photon excited fluorescence imaging of neural activity in the spinal cord of awake mice.* Abstract presented at the Society for Neuroscience Annual Meeting, San Diego, California.

Cheng, Y. T., Ness, S. L., Hu, S. H., Raikin, J., Pan, L. D., Wang, T., . . . Schaffer C.B. (2016). *In-vivo three-photon excited fluorescence imaging in the spinal cord of awake, locomoting mouse.* Abstract presented at the Optical Society of America Frontiers in Optics Conference, Rochester, New York.

Johnson, B. R., Lett, K., Dietz, S., Husch, A., & Harris-Warrick R. M. (2016). *Spinal neurons from adult mice do not show enhanced bistability after spinal cord injury in reduced calcium saline and elevated temperature.* Presented at the Society for Neuroscience Annual Meeting, San Diego, California.

Ness, S. L., Cheng, Y. T., Li, X., Cruz-Hernandez, J. C., Wang, T., Ouzounov, D. G., . . . Schaffer, C. B. (2016). *In-vivo three-photon excited fluorescence microscopy of the spinal cord in the awake, locomoting mouse.* Presented at the Biomedical Optics Conference, Fort Lauderdale, Florida.

6. Health Research, Incorporated

A Motion Lab Systems unit for locomotor analyses and a LLC Digitimer DS5 Computer Controlled Stimulator were purchased. These equipment items are improving the precision and specificity of the new therapeutic protocols that are being developed and they are enabling comprehensive detailed analyses of the functional impact of these new therapeutic protocols. They are thereby enhancing new clinical methods and their dissemination, and will substantially strengthen planned applications for further SCI research. Studies using this new equipment are currently in progress and publications will be forthcoming.

Funding also supported the projects of two principal investigators, Dr. Yu Wang and Dr. Johnathan S. Carp. Staff support was provided to researchers who were contributing to these SCI projects. The projects enabled and accelerated by this funding that are currently in progress:

- Dr. Wang's research project focuses on developing and validating novel operant-conditioning-based therapeutic methods for improving functional recovery after SCI.
- Dr. Carp's research project focuses on understanding the urinary dysfunction that occurs after SCI disrupts the normal role of the neurons that activate the external urethral sphincter muscle (EUS motoneurons).

7. Icahn School of Medicine at Mount Sinai

Funding was used to purchase new equipment and supplies, such as:

- Inverted microscope with camera (Olympus)
- Upgrade of upright microscope (Zeiss) with far-red fluorescent capability
- PCR machine (Biorad)
- Oxygen and carbon dioxide controller (Biospherix ProOx C21)

Funding also supported Dr. Hongyan Zou and nine other research staff. Dr. Zou's first project studied novel molecular and epigenetic mechanisms that govern axon growth potential of adult neurons. Dr. Zou's second project studied immune response in SCI models. The preliminary data generated through this funding was used to support future SCI applications for funding and has helped the researchers to generate two manuscripts:

Kuboyama, T., Huang, Y., Wahane, S., Wong, J., Koemeter-Cox, A., Martini, M., . . . Zou, H. (2016). *HDAC3 inhibition ameliorates spinal cord injury by immunomodulation*. Manuscript submitted for publication, Icahn School of Medicine at Mount Sinai.

Loh, Y. E., Koemeter-Cox, A., Finelli, M., Shen, L., Friedel, R. H., & Zou, H. (2016). Comprehensive mapping of 5-hmC epigenetic dynamics in axon regeneration. *Epigenetics,* 5, 1-6. doi: 10.1080/15592294.2016.1264560.

Researchers presented the following abstract at two international conferences on axon regeneration, neural plasticity and SCI:

Kuboyama, T., Huang, Y., Wahane, S., Wong, J., Koemeter-Cox, A., Martini, . . . Zou, H. (June, 2016) *HDAC3 inhibition ameliorates spinal cord injury by immunomodulation.* Presented at the Gordon Conference, Molecular and Cellular Neurobiology, Hong Kong China.

Kuboyama, T., Huang, Y., Wahane, S., Wong, J., Koemeter-Cox, A., Martini, . . . Zou, H. (September, 2016) *HDAC3 inhibition ameliorates spinal cord injury by immunomodulation.* Presented at the Axon Guidance, Synapse, Formation & Regeneration Meeting, Cold Spring Harbor, New York.

8. Regenerative Research Foundation

Funding was used to purchase new equipment and supplies, such as:

- Wafergen ICELL8 Single-Cell System that allows single-cell isolation through individual cell barcoding for cell registration and single cell transcriptome analysis
- Eppendorf refrigerated centrifuge to be used in the preparation of spinal cord cells
- Osmometer to improve the quality of the buffers and media used in the experiments
- Minus 80°C Thermo upright freezer
- Reagents and mice required to perform the immune cell isolation for transcriptome profiling

The research supported through this funding will provide the basis for future grant applications aimed at studies of immunomodulatory therapeutic approaches for SCIs.

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

Funding was used to purchase new equipment and supplies, such as:

- Wired AD Instruments and Wireless Trigno Delsys 16 Channel recording systems
- Digitmer DS7A constant current stimulator
- TSE treadmill system
- Computer controlled dynamic cold/hot plate
- Axon Digidata 1550B 8 channel digitizer
- Zeiss Stemi 305 EDU stereo-microscope with integrated illumination
- Magstim D70-2 coil

For each above mentioned equipment, computers were purchased in order to control the equipment separately. This equipment was used to accelerate an animal experiment using an animal SCI model. For this experiment, funds were used to provide supplies for production of stem cells by collaborator, Dr. Philip Horner, for improving the animal recording system. This funding was also used to build a setup for electrophysiological evaluation of spino-muscular circuity in non-injured and SCI humans.

Citations for publications or meeting abstracts that have been accepted as a result of the funding:

Alessi, V., Petrosyan, H. A., Sniffen, J., Sisto S. A., Kaufman, M., & Arvanian, V. L. (2016). *Transcranial magnetic stimulation (TMS) evoked responses from hind limb muscles are diminished in spinal cord injured animals and partially recovered following improved plasticity induced by repetitive electromagnetic stimulation at spinal levels.* Abstract presented at the Society for Neuroscience Annual Meeting, San Diego, California.

Arvanian, V. L., Petrosyan, H. A., Alessi, V., Phagu, N. P., Levine, J. M., & Collins, W. F. III. (2016). *Viral vector mediated neutralization of NG2 proteoglycan (AAV-NG2Ab) combined with delivery of neurotrophin NT-3 (AAV-NT3) improves transmission, locomotion and urinary tract function after incomplete spinal cord injury in adult rats.* Abstract presented at the Society for Neuroscience Annual Meeting, San Diego, California.

Petrosyan, H.A., & Arvanian, V.L. (2016). *Transmission from motor cortex to spinal cord neurons and limb muscles in intact and lesioned motor cortex of adult rats.* Abstract presented at the Society for Neuroscience Annual Meeting, San Diego, California.

Petrosyan, H. A., Alessi, V., Hunanyan, A. S., Sisto, S. A., & Arvanian, V. L. (2015). Spinal electro-magnetic stimulation combined with transgene delivery of neurotrophin NT-3 and exercise: novel combination therapy for spinal cord injury in rats. *Journal of Neurophysiology, 114*(5), 2923-40. doi:10.1152/jn.00480.2015.

Petrosyan, H. A., Alessi, V., Sniffen, J., Sisto, S. A., Fiore, S., Davis, R., . . . Arvanian, V. L. (2015). Safety of titanium rods used for spinal stabilization during repetitive magnetic stimulation. *Clinical Neurophysiology, 126*, 2405-6. doi: http://dx.doi.org/10.1016/j.clinph.2015.02.059.

10. Research Foundation of CUNY - City College

Funding was used to purchase new equipment and supplies, such as:

- A data acquisition for trans-cranial magnetic stimulation (TMS) motor assessment system
- Electrophysiological equipment for monitoring motor function and plasticity,
- Neuronal morphology system
- Workstation for image analysis and model stimulation for trans-spinal direct current stimulation and modeling of forces for feline SCI
- Instrumentation for assessing motor behavioral functions after SCI
- Transcriptome assay and RNA kit
- Microinjection pump and syringes
- A transgenic mouse line to assess functional connections of the damaged motor system
- An assortment of key research tools that enabled establishment of laboratory space in the CUNY animal facility

This funding also provided staff support for five laboratory scientists. As of this reporting period, there has been no dissemination of findings.

11. Research Foundation of CUNY - Staten Island

Funding was used to purchase new equipment and supplies, such as:

- A Bistim Module TMS Upgrade
- Double 110 MM TMS Coil
- DC Plus Stimulator
- Digitimer high voltage simulator
- Nanodrop Cycler
- Powerlab Acquisition System
- PCR Thermocycler

In Dr. Ahmed's laboratory, the equipment has been used to electromyographically evaluate the recovery of muscle activity following SCI in mice and testing the expression of certain RNA following SCI. The data resulting from these projects has been submitted for publication.

In Dr. Knikow's laboratory, the equipment purchased supported the projects listed below:

- Plasticity of human cortical neuronal circuits after transspinal direct current stimulation. A single-blind, sham-controlled, randomized crossover study.
- Neuroplasticity and recovery of motor function after transspinal stimulation in SCI.
- Changes in brain activity after transspinal stimulation.

Citations for publications or meeting abstracts that have been accepted as a result of the funding:

Knikou, M., Santora, D., Dixon, L., & Ibrahim, M. M. (2016). *Paired Transspinal and Transcortical Stimulation Associative Stimulation Modulates Human Spinal Motor Output.* Poster presented for the Spike-Timing Dependent Plasticity Session, Society for Neuroscience Annual Meeting, San Diego, California.

Murray, L. M., Tahayori, B., Chiacchiero, M., & Knikou, M. (2016). *Changes in motor function and reflex circuits with repetitive transspinal stimulation after spinal cord injury.* Abstract presented at the Exploring Treatment Strategies in Experimental Spinal Cord Injury Models Nanosymposium, Society for Neuroscience Annual Meeting, San Diego, C.A.

Smith, A. C., & Knikou, M. (2016). A Review of Locomotor Training after Spinal Cord Injury: Reorganization of Spinal Neuronal Circuits and Recovery of Motor Function. *Neural Plasticity,* 1216258. doi: 10.1155/2016/1216258.

Tahayori, B., Murray, L.M., Ahmed, Z., & Knikou, M. (2017). *Plasticity of human cortical neuronal circuits after transspinal direct current stimulation: A single-blind, sham-controlled, randomized crossover study.* Abstract presented at the Combined Section Meeting, American Physical Therapy Association, San Antonio, Texas.

12. Research Foundation of SUNY – Albany

This funding provided staff support to Principal Investigator, Dr. Ben Szaro, and two laboratory scientists. Dr. Szaro's laboratory studies SCI in tadpoles and frogs of the species *Xenopus laevis.* These animals are unique in that although they express all the genes known to inhibit central nervous system (CNS) axon regeneration in mammals, they nonetheless functionally recover fully from SCI as tadpoles, but they lose this ability as they metamorphose into frogs.

Funding was also used to purchase new equipment and supplies, such as:

- Nikon SMZ25 motorized fluorescence stereo microscope and imaging workstation
- Dell Precision Tower 7910 workstation
- Thermo Scientific Barnstead Smart2Pure UV/UF 3L/h4 water purification system

The equipment purchases were critical for all aims related to this project, which is pending publication.

13. Research Foundation of SUNY - Downstate Medical Center

All of the equipment purchased provide support for currently funded SCI research, toward making and testing a 24/7 Brain Machine Interface. Data from this work will be used as preliminary data for future SCI research projects.

14. Research Foundation of SUNY - Stony Brook

Funding was used to purchase new equipment and supplies, such as:

- 3-D microscope
- Cryostat
- Plethysmographs
- Collimaters

The microscope and cryostat have been used by the SCI Core facility for multiple projects related to SCI research. The plethysmographs will be used in future SCI projects. One of the two collimators purchased was already incorporated in the irradiation set up at the Division of Laboratory Animal Resources (DLAR) at Stony Brook. Histology was purchased to assist in obtaining pilot data on projects conducted between laboratories.

Principal Investigator, Dr. Prithvi Shah, recruited Dr. Nasrin Fatemi for expertise in spinal cord laminectomy procedures.

As of yet, no publications or meeting abstracts have been accepted. This is partly due to the multi-year timeframe for the successful completion of major projects which are being conducted by the SCI Core members.

15. Sloan-Kettering Institute for Cancer Research

This funding provided staff support to Principal Investigator, Dr. Urs Rutishauser. The main focus of Dr. Rutishauser's laboratory research is to engineer polysialic acid (PSA) on cell surfaces to promote tissue plasticity and repair following SCI.

Funding was also used to purchase new equipment and supplies, such as:

- AKTA Pure L1 FPLC machine
- MOXI-FLOW machine
- Tissue culture microscope
- Microinjection unit

This equipment supported many objectives in this SCI research project. Data generated using this funding will be made public through presentation in meetings and publication in scientific journals.

16. Syracuse University

Funding was used to expand on SCI research at Syracuse University for three principal investigators' objectives:

- Functions of Lbx and Skor Transcription Factors. Equipment was purchased to expand and improve the zebrafish facility for Dr. Katharine Lewis' research.
- In vivo real time changes in injured spinal cord measured with Raman Spectroscopy (RS). Funding was used to purchase a New York University, Multicenter Animal Spinal Cord Injury Study Impactor as well as surgical tools and supplies needed for Dr. Julie Hasenwinkel's research.
- Electrophysiological measurement of spinal circuit excitability pre and post SCI. Funding was also used for Dr. Shreckengost's research to expand the capabilities of Syracuse University to perform slice electrophysiology, fluorescent imaging and patch clamp electrophysiology.

Citations for publications or meeting abstracts that have been accepted as a result of the funding:

Hilinski, W. C., Bostrom, J. R., England, S. J., Juarez-Morales, J. L., de Jager, S., Armant, O,. . . Lewis, K. E. (2016). Lmx1b is required for the glutamatergic fates of a subset of spinal cord neurons. *Neural Development,* 11:16 doi: 10.1186/s13064-016-0070-1.

17. The Feinstein Institute for Medical Research

Funding was used to support Principal Investigator, Dr. Ona Bloom, and several staff members working on the research project titled, "Biomakers of Spontaneous Recovery from Traumatic Spinal Cord Injury". Since relatively little is known about the biological processes that influence physical recovery in people after SCI, the purpose of this project is to fill this gap in knowledge and advance the ability to predict and promote recovery for persons with SCI.

18. University of Rochester

This funding was used to accelerate and/or jumpstart eight projects related to the development of new treatments for SCI, all projects were carried out at the University of Rochester Medical Center:

- Six of these research projects focused on a variety of discoveries that hold promise for enhancing the ability to treat acute or chronic SCI,
- One research project focused on the development of improved approaches to the restoration of motor function, and
- One research project focused on motor rehabilitation in individuals with chronic SCI, and provided training required to incorporate best-of-practice utilization of transcranial magnetic stimulation in conjunction with robotics-based motor rehabilitation.

19. WM Burke Medical Research Institute

Funding was used to purchase a ThorLabs multi-photon microscope, which is being used to understand the response of the brain to spinal cord injury, rehabilitation, and repair. The microscope allows for the collection of data on both structure and neural activity within the brain and spinal cord in awake, behaving animals.

Appendix 2

Individual Predoctoral/Postdoctoral Fellowships (Round 1)

Contract Term 3/1/16 – 2/28/19

Progress Reporting Period 3/1/16 – 9/1/16

5 Awards, Procurement Total: $695,041

1. Rensselaer Polytechnic Institute

Ryan Gilbert, Ph.D., Christopher Johnson, D.L., B.S., Diana-Andra Borca-Tasiuc, Ph.D., Lee Lignon, Ph.D.
Predoc: $135,600
Project Title: Magnetic Alignment of Electrospun Fibers for Treatment of Acute Spinal Cord Contusive Injury

The principal investigator has yet to submit a progress report for this reporting period. This information will be included in the 2017 SCIRB Annual Report.

2. Research Foundation for SUNY, University at Albany

Ben Szaro, Ph.D., Rupa Choudhary, M.S., Melinda Larsen, Ph.D., Gregory Lnenicka, Ph.D., Kurt Gibbs, Ph.D., Cara Pager, Ph.D.
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. Our 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 this first reporting period, the trainee developed reagents and refined techniques for measuring expression of SOCS2 and SOCS3 proteins and mRNAs and has made reagents for inhibiting their expression in regenerating and developing CNS neurons. She is now beginning to collect data on expression of these genes at key time points after injury.

Future Directions: The trainee plans to finish expression studies of optic nerve injury, expand her studies to include tadpole and frog SCI, and to begin manipulating SOCS2 and SOCS3 expression in CNS injury and development.

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.

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: We have largely completed Aim 1 experiments, which determined if direct current (DC) stimulation promotes sprouting of CST axons in injured animals. Whereas we have found that cathodal DC stimulation strongly facilitates motor signals from the motor cortex, our present results suggest that direct current does not contribute to a CST sprouting response. For these experiments we chose a late time point following injury, when an injury-induced increase in reflex strength is present. We hypothesize that DC stimulation may interact with excitability changes in the spinal cord at this time point. Experiments for Aims 2 and 3 are in progress.

Future Directions: We plan to examine the effect of DC stimulation at different time points after injury and correlate the increased motor evoked potential (MEP) amplitude that we see with DC stimulation with the state of spinal cord excitability (assayed by H-reflex).

Citations for publications or meeting abstracts that have been accepted as a result of the funding:

Amer, A., Shakarov, G., Soliman, Y., & Martin, J.H. (2016). *Chronic theta burst electrical stimulation of rat motor cortex promotes CST outgrowth and M1-to-muscle connection strength.* Abstract presented at the Society for Neuroscience Annual Meeting, San Diego, California.

4. Winifred Masterson Burke Medical Research Institute

Jason Carmel, M.D., Ph.D., Caitlin Hill, 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 with limited functional recovery of hand movement by disconnecting the brain and spinal cord. While motor function is impaired, some connections are spared and provide potential substrate for therapeutic treatment. In this study, we aimed to identify

the connections responsible for spontaneous recovery among them and strengthen them to improve recovery.

Progress Toward Specific Aims: Our goal is to identify the connections responsible for spontaneous recovery of hand movement after spinal cord injury because we hypothesize that these are the best ones to electrically stimulate in order to strengthen them. To identify these connections, we trace them with a fluorescent protein delivered by virus. To prove whether these connections are necessary, we inactivate them using a technique that blocks electrical signals in specific connections.

To make labeling of nerve cell connections more specific and stronger, we adopted a new tracer injection method that uses electric current to deliver the tracers to the tissue. Various durations of electric current were tested and the correlation between current duration and labeling efficacy was obtained to control the strength of labeling precisely. Also, a new inactivation system was adopted. We are testing various conditions of applying the system to candidate connections to inactivate them without damage.

Future Directions: In the next period, first, we will confirm whether the injection condition of tracers with new delivery method labels the candidate connections strongly enough to analyze the anatomical changes of the connections in the spinal cord. Second, we will test if the selected delivery conditions of the new inactivation system are sufficient to inactivate the connections.

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

Citations for publications or meeting abstracts that have been accepted as a result of the funding:

Park, H. G., & Carmel, J. B. (2016). Selective Manipulation of Neural Circuits. *Neurotherapeutics,* 13(2):311-24. doi: 10.1007/s13311-016-0425-7.

5. Winifred Masterson Burke Medical Research Institute

Jian Zhong, Ph.D, Mariel Voutounou, Ph.D., Francesco Boato, Ph.D.
Postdoc: $165,354
Project Title: Promoting Intrinsic Growth Competency ofTtw Injured Neurons Using Genetic and Small Molecule Approaches

Introduction/Background: The failure of the adult CNS to regenerate severed axons is attributed a) to extraneuronal growth inhibitory molecules such as Nogo, MAG and OMgp, b) glial scar formation causing a barrier to axon extension, and c) the low intrinsic growth capacity of mature CNS neurons.

This study aims to maximize axon sprouting and regeneration after SCI in mice, by combining genetically enhanced neuron-intrinsic growth signaling with the suppression of extrinsic growth inhibitory cues. The ability of small molecule drugs to enhance intracellular growth signaling and promote axon regrowth after SCI will also be tested, as an initial step towards clinically relevant, non-genetic interventions.

Progress Toward Specific Aims: At this point, I have determined the proportion of cortical motor neurons that respond to the genetic manipulation that increases their growth capacity, and found that, as it should be, only these axons regenerate or sprout after SCI. I have learned to perform the T8 dorsal hemisection and crush injury surgeries reproducibly. I am currently performing data analysis on the first group of injured animals. I have also learned the unilateral pyramidotomy (UP) surgery, and am currently assessing the extent of sprouting after UP in positive and negative control animals.

Future Directions: I will determine to what extent elevated B-RAF signaling can promote regeneration in the absence of the myelin-based growth inhibitory molecules. In addition to the CST analyses, this will also include investigation of dorsal root axon regeneration after dorsal root crush. Furthermore, I will investigate the effects of certain small molecule drugs that activate the mitogen-activated protein (MAP) kinase signaling pathway on post-injury regeneration and sprouting of the CST.

Impact: The identification of a molecular strategy that can substantially promote axon growth in the injured cord, together with the identification of small molecules that could trigger this mechanism, will have a substantial impact on SCI regeneration research.

Appendix 2

CART/IDEA

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

Progress Reporting Period
6/1/16—10/31/16

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

1. Albert Einstein College of Medicine, Yeshiva University
Principal Investigator: David Sharp, Ph.D.
CART: $1,197,182
Project Title: Harnessing Microtubules to Enhance Urological Function after Spinal Cord Injury

The principal investigator has yet to submit a progress report for this reporting period. This information will be included in the 2017 SCIRB Annual Report.

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. Our 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. We 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 sysnthesis to facilitate NMJ maintenance. We 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. We are now focusing on the functional impact of these alterations.

Impact: We 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

propogation 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. We want to understand how to combine hand therapy (exercise) and electrical brain stimulation in chronic SCI. We hypothesize that training will be most effective delivered two weeks after electrical stimulation.

   Progress Toward Specific Aims: To promote functional recovery after injury, we 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. We decreased the training time by adjusting the protocol. We also increased the difficulty, which allows us to show deficits in rats, even though rats rely less on the spinal connection that we have to cut. We 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 we have successfully combined nerve cell tracers so we 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. We use a rat model of contusion injury of the upper part of the spinal cord, termed the cervical spinal cord. Our 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, we completed development of our SCI model. In the present reporting period we implemented our initial motor cortex-spinal cord stimulation plan.

   Progress Toward Specific Aims: We completed comparison of two animal groups in our 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.

We also examined the effect of trans-spinal direct current stimulation (tsDCS) on the spinal actions of motor and peripheral sensory fibers (Aims 2, 3; submitted for publication). We found significant, albeit minimal, suppression of the sensory fiber response by anodal stimulation and little or no effect of cathodal tsDCS. By contrast, we found strong significant facilitation of the motor response by cathodal stimulation and minimal suppression by anodal stimulation.

Our 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, we plan to complete the first contusion injury study and further pursue study of the interactions of sensory fibers and the corticospinal system (Aim 2). We also plan to begin modeling of the contusion injury to optimize spinal electrode development (Aim 3). If successful, the impact of our studies will include establishment of a minimally-invasive spinal neuromodulatory therapy for humans that targets the corticospinal system.

5. Health Research, Incorporated

Principal Investigator: Johnathan 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. We 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, we performed spinal injuries in rats for use in drug evaluation experiments, which are currently in progress. We 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 our laboratory, refining our experimental design, and beginning experiments, we 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. We focus on studying the potential therapeutic effect of a specific HDAC3 inhibitor in promoting functional recovery after SCI.

Progress Toward Specific Aims: We have conducted a time course study to further characterize the expression dynamics of HDAC3 after SCI. We have expanded our 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, we demonstrated a dampening of cytokines at the injury milieu and downregulation of inflammatory genes in the innate immune cells with HDAC3 inhibition.

Future Directions: We will deepen our mechanistic understanding of the role of HDAC3 in mediating the innate immune response after SCI. Specially, we will investigate the HDAC3-regulated gene network in microglia and macrophages in SCI.

Impact: Our study will validate HDAC3 as a critical epigenomic regulator that integrates injury signals to calibrate the innate immune response after SCI. Our 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: We aim to improve function of spared nerve circuits after spinal cord injury (SCI) through the use of electrical and magnetic stimulation.

We 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, we 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 subjects with SCI have undergone CES testing. No serious adverse events have occurred. Two subjects had minor skin irritation at the site of stimulation.

We 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, we 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: We 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 or meeting abstracts that have been accepted as a result of the funding:

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. We have developed bioengineered micro-sized beads made of a biodegradable, biocompatible and FDA approved material. We 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 we have generated both SHH and IL10 pDNA microbeads and demonstrated their activity in vitro. In addition, we 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 we plan to study the effect of IL10 pDNA microbead delivery on functional locomotor and histological recovery in acute and chronic SCI. We 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 our 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. We 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 we 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, we 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 we are now setting up the full BMI system to work with the wireless recording and the wireless recording/stimulation systems. We will be integrating systems from Blackrock Microsystems as well as Triangle Bio-systems. Once the implant design is finished we will be implanting our first animal, which we expect to do in the next two months.

Future Directions: Over the remainder of the project. We 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 we 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 we implant such systems into humans.

Citations for publications or meeting abstracts that have 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, 2016

[1] Service concluded during 2016
[2] Service commenced during 2016

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

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

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

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

David A. Carmel [1]
Carmel Asset Management, LLC

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

Bernice Grafstein, Ph.D., DSc
Weill Medical College of Cornell University
Department of Physiology and Biophysics; Department of Neuroscience; Brain and Mind Research Institute

Keith Gurgui
Resource Center for Accessible Living

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

Gary D. Paige, M.D., Ph.D.
University of Rochester Medical Center
Department of Neurobiology and Anatomy

Fraser Sim, Ph.D.
University at Buffalo
Department of Pharmacology and Toxicology

Mark Menniti Stecker, M.D., Ph.D. [1]
Winthrop University Hospital
Department of Neuroscience

Adam B. Stein, M.D.
North Shore-Long Island Jewish Health System
Department of Physical Medicine and Rehabilitation

Wadsworth Center, Extramural Grants Administration

Victoria Derbyshire, Ph.D.

Teresa K. Ascienzo

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Andrea Garavelli [2]

Jeannine M. Tusch

Carlene Van Patten

Division of Legal Affairs
Bureau of House Counsel

Diana Yang, J.D. [1]

Joan K. Harris, Esq. [2]