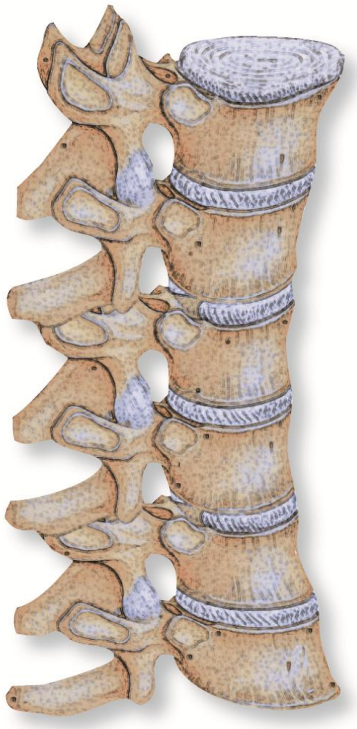
NEW YORK STATE | Department of Health
Wadsworth Center



SPINAL CORD INJURY RESEARCH BOARD

# NYS SCIRB Annual Report

January 1, 2024, to December 31, 2024

## 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 neurorehabilitation, 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 1,100 New York residents suffer traumatic SCIs[1] joining approximately 305,000 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 SCI Statistical Center reported that first-year costs for an individual with SCI range from approximately $447,037 to more than $1,369,755, with annual costs thereafter ranging from approximately $54,298 to $237,862.[2] These expenses are borne by 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, 2019 data

2 "Spinal Cord Injury Facts and Figures at a Glance." *National Spinal Cord Injury Statistical Center.* University of Alabama at Birmingham, 2024. Web. 29 August 2024. 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 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, Wadsworth Center, and Extramural Grants Administration 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 the Wadsworth Center's website: https://www.wadsworth.org/extramural/spinalcord.

The SCIRB appreciates the opportunity to serve the citizens of New York State by focusing on the 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). By the end of 2024 the current composition of the SCIRB included three (3) researchers, six (6) clinicians, and two (2) spinal cord-injured persons. Members serve four-year terms. One (1) new appointment was made in 2024, and three (3) vacancies include one (1) to be filled by the Governor and two (2) to be filled by the Speaker of the Assembly.

## III. SCIRB OPERATIONS

In State Fiscal Year 2024-25, $8.5 million was programmed to support SCI research.

The SCIRB held two (2) meetings in 2024 (see Section IV below). By the end of 2024, three (3) procurements had been released by the New York State Department of Health, Wadsworth Center, Extramural Grants Administration on behalf of the SCIRB.

Meetings are announced at least one week in advance whenever possible and are open to the public (in-person and virtually) in accordance with Open meetings law (Article 7 of the Public Officers Law). Meeting agendas are posted on the Wadsworth Center's Website at: https://www.wadsworth.org/extramural/spinalcord/meetings.

A recording of each meeting is available via the Department of Health's public Website https://www.health.ny.gov/events/webcasts/archivew/ for at least 30 days after the meeting, opening the proceedings to a wide audience.

The SCIRB Bylaws were amended in 2024 to updated language to be homogenous with Open Meetings Law and to include the newly adopted provisions found within Section 103-a(c). The bylaws can be found at https://www.wadsworth.org/extramural/spinalcord/advisory-board/statutes-bylaws.

## IV. MAJOR ACTIVITIES OF THE SCIRB

### *Business Meetings*

At its **March 22, 2024**, meeting, the Board welcomed Dr. Avinash Mohan to the Board. He had been appointed to the Board in 2023, and this was his first meeting. The SCIRB voted and recommended funding for zero (0) awards from the Translational Research Projects in Spinal Cord Injury (Round 5) Request for Applications (RFA) for a total of $0 (zero dollars). They also voted to update the Board's bylaws to be homogenous with Open Meetings Law § 103-a allowing for members with disabilities to attend meetings virtually while remaining eligible to count towards quorum.

At its **November 15, 2024**, meeting the Board welcomed Dr. Ramin Rak who replaced Dr. Bernice Grafstein. The SCIRB recommended funding for nine (9) awards from the "Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activates (IDEA) in Spinal Cord Injury (Round 7)" Request for Applications (RFA) for a total of $5,467,285. These five (5) (IDEA) and four (4) (PART) year awards began in July 2025.

A tabular summary of these procurements can be found in Appendix 1.

### *Previously Recommended SCI Research Contracts*

In July 2024, thirteen (13) Institutional Support for SCI Research in New York State (Round 7) contracts began their second year. The scientific progress resulting from these five (5) year awards can be found in Appendix 2.

In September 2024, eight (8) Predoctoral and Postdoctoral Fellowships in Spinal Cord Injury Research (Round 5) contracts began their final year. The scientific progress resulting from these two (2) year awards can be found in Appendix 2.

By November 2024, one (1) PART award from Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activates (IDEA) in Spinal Cord Injury (Round 4) completed their final year. The scientific progress resulting from these three (3) year awards can be found in Appendix 2.

By October 2024, four (4) IDEA awards from Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activates (IDEA) in Spinal Cord Injury (Round 5) contracts completed their final year. One (1) IDEA award from Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activates (IDEA) in Spinal Cord Injury (Round 5) requested a 12-month contract extension. In October 2024, four (4) PART awards from Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activates (IDEA) in Spinal Cord Injury (Round 5) began their final year. The scientific progress resulting from these two (2) and three (3) year awards, respectively, can be found in Appendix 2.

In October 2024, four (4) IDEA and four (4) PART awards from Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activates (IDEA) in Spinal Cord Injury (Round 6) contracts began their second year. The scientific progress resulting from these two (2) and three (3) year awards, respectively, can be found in Appendix 2.

In October 2024, two (2) awards from Translational Research Projects in Spinal Cord Injury (Round 4) contracts began their second year. The scientific progress resulting from these four (4) year awards can be found in Appendix 2.

### *Funding Opportunities*

- Predoctoral and Postdoctoral Fellowships in Spinal Cord Injury Research (Round 6)
- Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activities (IDEA)in Spinal Cord Injury (Round 7)
- Translational Research Projects (TRP) in Spinal Cord Injury (Round 6)

### *NYS SCI Research Symposium*

The SCIRB discussed scheduling a future NYS SCI Research Symposium at their business meetings in 2024. A future symposium would highlight recent advances and developments in basic and translational SCI research, feature presentations of the research supported by the Program, and invite international/national speakers to present new discoveries.

A subcommittee was created to investigate the feasibility of holding a Symposium includes four SCIRB members and a representative from NYS Department of Health, Wadsworth Center, Extramural Grants Administration to act as a liaison for the Department of Health. This subcommittee met twice during 2024 in a preliminary capacity.

*Appendix 1*

**Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activities (IDEA) in Spinal Cord Injury (Round 7)**

| Organization | PI | Project Title | Recommended Funding |
|---|---|---|---|
| The State University of New York at Buffalo | Hang Jin Jo, Ph.D. | Neuromodulation to Improve Grasping Function After Spinal Cord Injury | $357,582 |
| The Feinstein Institutes for Medical Research | Ona Bloom, Ph.D. | Tolerability and preliminary efficacy of galantamine to treat metabolic syndrome in people with chronic spinal cord injury (SCI) | $340,577 |
| The State University of New York at Albany | Janet L. Paluh, Ph.D. | Molecular and Functional Outcomes of Combined Epidural Spinal Stimulation and Neuron Interneuron Excitatory Ribbons | $905,044 |
| The City College of New York | John Martin, Ph.D. | Combined biomaterial scaffold - neuromodulation strategy for recovering function in preclinical model of rodent SCI | $990,000 |
| Icahn School of Medicine at Mount Sinai | Leif A. Havton, M.D., Ph.D. | AI-Guided Predictions of Blood Pressure Dysregulation using Perfusion Index as a Novel Biomarker in Persons with Spinal Cord Injury | $926,228 |
| Bronx Veterans Medical Research Foundation | Carlos A. Toro, Ph.D. | Parenterally administered formulations of boldine to preserve function after SCI | $345,000 |
| The Research Foundation for CUNY Staten Island | Maria Knikou, P.T., M.B.A., Ph.D. | Cervical and Lumbosacral Transspinal Stimulation to Reconnect the Injured Human Spinal Cord | $922,983 |
| Icahn School of Medicine at Mount Sinai | Hongyan Zou, M.D., Ph.D. | Transcriptional regulator of axon regeneration in SCI | $360,000 |
| Sunnyview Hospital and Rehabilitation Center | Amy E. Teale, Ph.D. | Effectiveness of Sensorimotor Versus Motor-Only Training in Restoring Upper Limb Sensory and Motor Function for Patients with Spinal Cord Injury: A Comparative Study | $319,861 |
| | | **Total (9 Awards)** | **$5,467,285** |

*Appendix 2*

## Scientific Progress Resulting from SCI Research Board Funded Projects

**Institutional Support for SCI in New York State (Round 7)**
**Contract Term 07/01/2023-06/30/2028**

**Progress Reporting Period**
**07/01/2024-12/31/2024**

**13 Awards, Procurement Total: $3,900,000**

### 1. Winifred Burke Medical Research Institute

Funding was used to support the Core Manager at the Structural and Functional Imaging Core at Burke Neurological Institute (BNI). The Structural and Functional Imaging Core is used by all SCI researchers at BNI to produce scientific results and discoveries, support future funding applications, and generate high quality images for scientific talks and publications.

Several pieces of equipment (including an Inscopix nVoke Miniscope System, an upgrade for an existing Leiss LSM 710 microscope, software licenses, and a Nikon CF175 APO 25X objective) have been purchased with SCIRB funds. This equipment has been used in support of new applications to NIH offerings as well as scientific meetings and publications.

### 2. The Research Foundation for SUNY – Stony Brook

Several pieces of equipment were purchased using the SCIRB funds: *Keyence Plan Apochromat BZ40x Objective for BZX All-in-One Fluorescence Microscope System*, *Nikon Plan Achromat 1x Objective for BZX All-in-One Fluorescence Microscope System, Leica Anti-roll Plate Assembly, Qsonica Q125 Sonicator Ultrasonic Homogenizer System and a HTEC-600 All-in-One Stand-Alone HPLC-ECD system with Clarity Data System Analysis Software.*

Equipment is being used in a collaborative pilot project to continue to obtain preliminary data investigating serotonin-dependent BDNF pathway-mediated neuroplasticity in histological sections of lumbosacral spinal cord regions controlling bladder function in response to novel task-specific training in bladder function. The new Biochemical Assay/Analysis Core equipment (ultrasonic homogenizer) are currently being used to process lumbosacral spinal cord tissue samples to obtain total protein homogenates that will be used to obtain preliminary biochemical assay data for this pilot project. Once additional histological data and preliminary biochemical assay data are obtained in this pilot project, the preliminary findings will be presented at a scientific conference (*e.g.*, American Physiology Summit 2025, American Urological Association 2025, or Society for Neuroscience 2025).

### 3. The Research Foundation for SUNY – Downstate Health Sciences University

Funding was used to support a Postdoctoral Researcher's effort on a project aims to leverage the most detailed biophysical model of motor cortex (M1) neural circuits to characterize how low-dimensional latent dynamics, associated with behavior, are represented in EEG signals. This research has contributed to an R01 grant proposal submitted to NIH "AI-based automated development of multiscale brain circuit models" and the creation of a Center for AI in Mental Health, funded by the SUNY STRIVE program.

Research supported through this funding will provide unprecedented insights into how the different neural populations and cell types within M1 contribute the latent dynamics neural manifolds. It will address a long-standing question regarding whether these behavior-related latent dynamics are encoded in the EEG signals, since most BMI for SCI patients employ non-invasive recording of EEG. These results will pave the way for multiple new avenues of research, including the encoding of behavior in M1 neural circuits and EEG signals, the stability of latent dynamics across animals and the development of improved BMI decoders.

**4. Bronx Veterans Medical Research Foundation**

Equipment purchased in Year 1 of the award has been installed in the mouse procedure room in the vivarium. Studies supported by the equipment include understanding the effects of a multi-drug treatment regimen on tracts that survived SCI.

Equipment purchased with SCIRB funds included a Motorized Moust Sterotaxic Frame with Joystick and aQuintessential Sterotaxic injector. The research team will utilize tract tracing to understand how treatments or genetic manipulations alter neural circuitry after spinal cord injury using this equipment and will also be used in studies seeking to understand effects of a multi-drug treatment regimen on tracts that survived SCI. Data analysis for this project is on-going.

**5. Icahn School of Medicine at Mount Sinai**

Funding was used to support staff, and lab supplies to enhance understanding how glial cells respond to spinal cord injury to build a protective glial barrier around lesion cord in critical. Researchers have been conducting additional experiments to address the reviewer's critiques, in particularly additional single nuclear RNA-sequencing, and generation of conditional knockout of Plexin-B1 to pinpoint cell type-specific effect in astrocytes. Researchers are in the process of preparing resubmission to *Nature Neuroscience*.

The data generated from this funding will be used to prepare *future NIH R01* grant application to further understand how astrocyte and microglia communicate with each other. The study supported by this funding allows researchers to utilize advanced live cell imaging and time lapsed videography to capture how glial cells resolve collision, extend and retract long processed, and organize with one another.

Funding from SCIRB has been used in supporting staff and lab supplies for spinal cord injury studies. They have made great progress towards understanding the molecular mechanisms of astrocytosis in response to spinal cord injury. The data generated from this funding will be used to prepare *future NIH R01* grant applications to further understand cell-cell communicate in response to spinal cord injury. The study supported by this funding allows the team to utilize advanced live cell imaging and time lapsed videography

to capture how glial cells resolve cell collision, dynamically extend and retract long processes, and spatially organize against one another.

## 6. Regenerative Research Foundation

Sensory and motor testing equipment has been purchased allowing for injections of a virus expressing an intrabody against a-syn was injected into the spinal cord. Preliminary testing of the sensory equipment was performed. Stereo Investigator (SI) was used to quantify changes in the spinal spinal cord in response to a pharmacological intervention. The motor equipment and RNAscope equipment purchased in June and have not yet been used. Data generated from the equipment will be used to support the ongoing DoD and CHNF projects and to genereate data to support an upcoming grant application by Dr. Hill to the National Institutes of Health to continue her lab's research on spinal cord injury repair.

Sensory testing equipment was purchased included a von Frey aesthesiometer (Ugo Basile) and Hargreaves apparatus (IITC) and associated platforms and animal containment boxes. The motor function testing equipment purchased included a CatWalk Gait Analysis System (Noldus) and a Foot Misplacement Apparatus (Bioseb In Vivo Research Instruments). This equipment will support ongoing SCI studies funded by the Craig H. Neilsen Foundation (CHNF) entitled Assessment of bifunctional intrabodies against alpha-synuclein for SCI repair (CHNF-998945).

Funds were used to partially support Dr. Hill's (Principal Investigator) salary. These funds have enabled her to work on grant writing and generating preliminary data (staining and examination of tissue sections) for a follow up study to prior work (PMCID: PMC9635187), complete work associated with obtaining the necessary regulatory approvals for SCI studies (IACUC and IBC), and manage the SCI studies at the RRF.

Dr. Hill's lab is dedicated to spinal cord injury repair and the development and preclinical testing of interventions to promote recovery from SCI. Partial funding of Dr. Hill's salary allows her dedicated time to write, generate new ideas, maintain regulatory compliance and perform experiments necessary to generate preliminary data that will be used to submit an upcoming grant application.

## 7. University of Rochester

Funding was used to add new capabilities and upgrade existing resources. This included the purchase of a video guided, electronic von Frey system to enhance the accuracy of sampling test locations and help to speed up the training of users. Funding was also be used for computer upgrades for Catwalk system and the purchase of a dedicated ultralow freezer for tissue sample storage. Funding was used to purchase an improved spinal column mount for IH400 and ESCID device and an ultrasonic cleaner to preserve the longevity of high-grade surgical tools (such as micro rongeurs) as well as assist in the purchase of a low oxygen incubator for the culture of cells prior to transplantation into SCI animals.

SCIRB funding has been used primarily for personnel support and equipment purchases. This equipment includes Animal Behavioral Equipment, Surgical equipment, Tissue sample storage, tissue procession for histological analysis, Image analysis, and stem cell cultures.

Work supported by the Year-1 phase of ISSCI7 was used to support SCI research program from the NYS DOH and to submit new applications to the NIH

**8. Research Foundation of CUNY – Staten Island**

Equipment was purchased and installed to support SCI research and especially to develop a lab station for bladder studies after transspinal stimulation and locomotor training in people with SCI.

Researchers used the equipment to record transspinal evoked potentials in people with SCI during assisted stepping with the Lokomat. Further, the sterilization equipment was used for urodynamics tests performed in people with SCI after transspinal stimulation for recovery of somatic and non-somatic functions. The equipment will support grant applications to the NIH and DoD on bladder control and transspinal stimulation in SCI.These funds supported part of salaries for a lab manager/research associate, Mr. Shammah Solomon, and two post-doctoral research fellows, Dr. Andreas Skiadopoulos and Dr. Abdullah Sayed Ahmad. Currently, funds support the salary of Dr. Abdullah Sayed Ahmad, MD. All staff took part in experiments performed at the Klab4Recovery, scheduling of patients, maintenance of IRB documents, consent forms and stipends of subjects for this project.

**9. The Feinstein Institute for Medical Research**

Funding supported salaries and the purchase of equipment and supplies, 3 separate projects that aim to improve the understanding of factors that influence health and physical function in persons with traumatic spinal cord injury (SCI). Funding for Project 1, “Immunological Profiles in Veterans with Chronic SCI” will assist in performing systemic immunological profiling of Veterans with chronic SCI (PI: Bloom) and to explore potential correlations with anti-COVID antibodies measured in samples from the same individuals. Funding for Project 2, “Vaccine Responsiveness in People with SCI” will be used to assist in expanding inclusion criteria beyond that of a funded DOD study, (W81XWH2211032, Biomarkers of Immune Dysfunction and Vaccine Responsiveness in People with Chronic Traumatic SCI, (SCIVAX)" (PI: Bloom). Funding will partially support inclusion of persons with SCI who satisfy all other inclusion/exclusion criteria, and present at the Dept. of Physical Medicine and Rehabilitation outpatient SCI clinic for a flu or COVID-19 vaccine/booster to promote their health, but are less than one year from initial injury Funding for Project 3 (PI: Song), “Low intensity trans-spinal focused ultrasound stimulation (tsFUS) for the treatment of neuropathic pain” will be used to assist with the study the mechanism of tsFUS in the spinal circuit, and to develop a novel neuromodulation strategy for pain control after spinal cord injury.

The goal of the research is to increase knowledge of biological processes that influence neurological recovery and important medical consequences, such as infections and neuropathic pain, in persons with SCI. The data collected with NYSCIRB support will enable the teams to fill gaps in knowledge needed to promote recovery and health in persons with SCI. Data collected from these projects will be used to provide support of feasibility and scientific rationale for larger grant applications in SCI research.

**10. Rensselaer Polytechnic Institute**

Funding was used to support the staff hire of Dr. John Leman. Dr. John Leman has been instrumental in the development of poly(pro-estrogen), poly(pro-curcumin), and poly(pro-boldine) bionaterials for neural applications. In this role, he has synthesized polymer and developed new platforms to shape the polymers into appropriate shapes for application to in vivo animal models for investigation.

The grant has also been used to support the projects for graduate students pursuing their Ph.D. work. Graduate students Payton O'Connor has used funds to promote her project to develop materials to alter astrocyte response following SCI. Jack Devlin has used some funds to support the development of drug delivery tools for neural applications. Derek Nelson has used some funds to support his development of mRNA-delivery materials and hydrogel biomaterials for drug delivery to the nervous system. The support for these graduate student projects were used to buy supplies and support their travel to the biomedical engineering society meeting. Funds will also be used in the development of future NIH R21 applications.

**11. The Trustees of Columbia University in the City of New York**

Funding will be used by the Robotics and Rehabilitation Lab at Columbia University to develop robotics for trunk and neck control for measurement and active control, with the goal of investigating the coordination and control of head and trunk motion while sitting and standing during tasks performed in augmented reality. Funding will assist with the characterization of spinal cord injury patients and compare with age-matched healthy adults. Funding will be used by the Movement Recovery Lab at Columbia to test multi-segment spinal cord stimulation to uncover its principles and maximize selectivity of individual muscles in rats.

**12. Research Foundation of CUNY obo City College of New York**

Funding was utilized to support salary of Martin Laboratory members including technician, fellows and graduate research assistants. Their work will help to advance ongoing SCI-related concepts and efforts in the lab.

Equipment was purchased for experiments involving the use of brain and spinal cord stimulation approaches (neuromodulation) to promote axon outgrowth and recovery after injury. Equipment also was purchased for imaging axon growth and for quantifying recovery of locomotor behavior after injury. To analyze the effect of neuromodulation on axon growth, researchers image the axons using a high-resolution RGB camera that interfaces with our axon analysis program (Microbrightfield NeuroLucida), which was purchased with SCIRB infrastructure support. The principal outcome of these microscopy studies is to promote axon growth after SCI. Use of this camera enables precise measurement of axon length in animals subjected to neuromodulation, in comparison with non-stimulated rats.

A key outcome of neuromodulation experiments is to promote improvements in motor function after SCI. The Research Team is using the Digigate treadmill and analysis system. Researchers needed to upgrade the cameral for monitoring locomotor behavior. With the purchased RGB camera researchers were able to precisely monitor changes in locomotor behavior before and after SCI and after therapeutic interventions. These improvements will continue to support ongoing SCI-related research in the Martin lab and at the CUNY School of Medicine.

**13. Albany Research Institute, Inc.**

Funding has been used to support research personnel who have been working on to assist the National Center for Adaptive Neurotechnologies (NCAN) in developing and disseminating novel non-invasive therapies that produce recovery of function after spinal cord injury (SCI). As a result of this funding personnel have been developing the new conditioning protocol, applying it in people with pain due to incomplete SCI, and using objective measures to establish that this new therapy reduces pain. Research personnel supported by this funding also worked to operantly condition EEG sensorimotor rhythms (SMR) to target beneficial plasticity that improves motor imagery and thereby improves motor recovery by developing a motor imagery conditioning (MIC) protocol, applying it to people with motor impairment due to SCI, and using objective measures of movement speed and accuracy to establish that this therapy restores motor function. Finally, research personnel also assisted in using stimulation to restore locomotion in rats with incomplete SCI by developing and applying the stimulation protocol in rats with chronic incomplete SCI and using objective measures of locomotor symmetry and speed to establish that this new therapy restores locomotion.

**Predoctoral and Postdoctoral Fellowships in Spinal Cord Injury Research (Round 5)**
**Contract Term 09/01/2023-08/31/2025**

**Progress Reporting Period**
**03/01/2024-08/31/2024**

**8 Awards, Procurement Total: $1,221,359**

1. **Winifred Burke Medical Research Institute**
   Yutaka Yoshida, Ph.D.; Alzahraa Amer, Ph.D., P.T., Applicant Fellow, Teruko Danjo (replacement Fellow)
   Postdoctoral: $180,581
   Restoration of Motor Function Following SCI Via Optical Stimulation

   Introduction/Background: Spinal cord injury (SCI) severs communication between the brain and motor circuits in the spinal cord resulting in paralysis. Restoring movement by repairing damaged motor pathways after SCI requires reestablishing motor circuits and having the brain learn to use these circuits for effective control.

   Some spontaneous motor recovery occurs by the formation of de-novo spinal detour pathways, bypassing the lesion site to the injured spinal cord. However, key aspects of limb motor control, such as movement trajectory, accuracy, and speed, rarely recover on their own. Researchers use a novel minimally invasive neuromodulatory paradigm to selectively target a class of spinal neurons, called V2a, that uniquely encodes these movement features in mice. Researchers hypothesize that increasing the activity V2a spinal neurons following SCI will enable the brain to have better moment-to-moment control of movement.

   During this period, an original applicant, Alzahraa Amer, had to move to Chicago due to her personal reason. Therefore, the fellowship has been transferred to Teruko Danjo. She has both MD and PhD and has interest in promoting motor recovery of human SCI patients. Since SCI research is new to her, she started learning SCI from members in Yoshida lab. So far, she has successfully set up the optogenetic stimulation in the cervical spinal cord.

   Progress Towards Specific Aims: Aim 1: Determine whether and how optogenetic stimulation of Chx10 causes anatomical changes of corticospinal circuits after SCI.
   Aim 2: Determine whether and how optogenetic stimulation induces motor recovery after SCI. During this period, the focus was on setting up skilled reaching and grasping behaviors after the cervical spinal cord injury.

   Impact: Plan to use the optogenetic system after SCI and perform both anatomical behavioral analyses.

2. **Columbia University**
   Jason B. Carmel, M.D., Ph.D.; Windsor KC Ting, Applicant Fellow
   Postdoctoral: $190,000
   Functional Dissection of the Rat Corticoreticular Pathway in SCI

Introduction/Background: Spinal cord injury can be debilitating, and for patients, recovery of fine motor function is a top priority. Researchers proposed to study the corticoreticular pathway using neural dissection techniques and assess the effect of activating and inhibiting this pathway on fine motor function, in healthy rodents as well as after spinal cord injury.

Progress Towards Specific Aims: Researchers made significant progress to determine the necessity and sufficiency of the interconnected corticoreticulo spinal pathway in motor function in healthy rats. For necessity, Researchers developed a superior, scalable pipeline to assess fine motor function. Regarding sufficiency, Researchers have strong evidence suggesting that electrical activation of the reticulospinal component of this pathway is sufficient to immediately augment motor responses under anesthesia.

Impact: This work helps us to understand the neural circuits implicated in normal and injured fine motor function in rodents, which they hope to directly translate to more effective treatment in humans. Support to do this work and to train as a postdoctoral fellow at Columbia is in large part due to this opportunity by NYS.

3. **The Research Foundation of CUNY obo City College of New York**
John H. Martin, Ph.D.; Jasmine Pathan, Applicant Fellow, Thelma Bethea, Current Fellow
Predoctoral: $118,000
Activity and Connectivity Maintain Premotor Interneuron Viability After SCI

Introduction/Background: The corticospinal system is essential for skilled movements in humans and many animals. Spinal cord injury (SCI) disconnects the motor cortex, which initiates movements, from the spinal motor circuits that integrate brain signals to produce movements. In addition to upper limb muscle weakness and loss of voluntary control after SCI, hyperreflexia is a key gain-of-function impairment that disrupts control of arm and hand movements. Hyperreflexia also can be produced by selective lesion of the corticospinal tract (CST), as a mechanistic model for hyperreflexia after SCI.
Two major mechanisms underpin hyperreflexia: (1) stretch reflex circuit changes produced by 1A fiber sprouting. together with reduced GABAergic inhibitory presynaptic regulation (GABApre); and (2) increased intrinsic motor neuron excitability produced by reduced motor neuron membrane-bound potassium-chloride co-transporter2 (KCC2). In this project we selectively lesioned the CST, a standard mechanistic model for SCI, and determined the mechanisms underlying hyperreflexia

Progress Towards Specific Aims: During the reporting period, Fellow Jasmine Pathan successfully defended her thesis and left the fellowship. For the remainder of the contract (beginning 10/1/24) the Fellow position was filled by Thelma Bethea. During their studies, they observed significant hyperreflexia in the contralesional forelimb only. Membrane-bound KCC2 was unchanged in in all motor neurons tested. Whereas both cervical and lumbar motor neurons showed increased 1A afferent sprouting contralesionally, there was a concomitant increase in GABApre terminals for the lumbar not cervical cord, which associated with a normal hindlimb H-reflex.

Impact: Researchers have, for the first time, used motor cortex neuromodulation to abrogate hyperreflexia and strengthen motor cortex-to-muscle connectivity. This can be translated to the human using non-invasive TMS, instead of epidural electrical stimulation.

**4. Rensselaer Polytechnic Institute**

Ryan J. Gilbert, Ph.D.; Edmund F. Palermo, Ph.D.; Adelle Hamilton, Applicant Fellow
Predoctoral: $122,400
Novel Poly (Pro-Gabapentin) Films to Provide Neuroprotection and Increase Neurite Extension

Introduction/Background: Neural interfaces link the nervous system with the outside world via electrodes, and offer the possibility of helping people with severe sensory and motor disabilities, like those who have suffered from spinal cord injury (SCI). Following electrode insertion into the brain, the tissue gets sheardd and free radical speceis are released which leads to neuronal death and glia activation, preventing proper interface between the electrodes and healthy brain tissue. Curcumin, a naturally occuring molecule, has antioxidant and anti-inflammatory properties and when used in polymer form, could act as an electrode coating.

Progress Towards Specific Aims: Continuing the poly-pro-curcumin project, researchers have since begun to electrospin P75. P75 electrospun fibers can offer enhanced cell migration and axonal outgrowth parallel to the alignment of the fibers. In addition, due to fibers having a high surface-area-to-volume ratio, P75 can offer high offer higher amounts of curcumin for a longer periods of time compared to its counter parts P25 and P50. Previously this polymer has never been electrospun so the majority of our time has been involving troubleshooting electrospinning parameters such as viscosity of the P75 solution, voltage, and the film material. Our lab has well established parameters for electrospinning PLA and have compared a PLA 8% solution to that of P75 12%, 16%, 20%, 22%, and 24%. Weight percents 16% and higher formed a gel and thus, were eliminated as candidates as they are not suitable for our electrospinning conditions. From this rheology data it was determined that a P75 12% would be the best place to start as it was the closest match to the viscosity of the PLA 8% solution.

P75 12% was first tested at our normal electrospinning conditions (15kV, 4cm gap distance, 400rpm, 8-9% humidity, and a 2mL/hour flow rate) on either 4% P75 or 4% PLA films. The results were inconclusive as no fibers were made at 15kV. Next, a 16kV voltage was used with a P75 12% on just 4% PLA films to not waste curcumin on films. From this experiment, the curcumin solution did not stick down to the PLA films and in fact only stuck to the mandrel. Though, it looked like fibers were made so this voltage will be experimented with again with a different substrate as the film. Either P75 film or a P75/PLA film will be tested to better warrant sticking of fibers to the film itself. Going forward, 16kV and 18kV will be tested in order pull the P75 solution out of the needle to form fibers onto the films.

Impact**:** Researchers believe the impact of the project will be in the synthesis of poly(pro-drug) forms of curcumin. Such pro-drug forms may not only negate reactive species but also act as a guidance cue to direct the migration of cells following spinal cord injury.

**5. Columbia University**

Sunil K. Agrawal, Ph.D.; Priya Kulkami, Applicant Fellow
Predoctoral: $116,000
Improving Trunk and Neck Coordination During Reaching Tasks with a Robotic Neck Brace in Individuals with Spinal Cord Injury

Introduction/Background: High thoracic and cervical spinal cord injury (SCI) can affect both postural control as well as head-trunk coordination. Since head and trunk coordination is known to be very important during reaching tasks, this coordination should be studied in both healthy subjects and those affected by SCI. The insights yielded by this study may be used to improve this coordination in patients with spinal cord injury. Using a robotic neck brace to provide external forces during reaching can assist this coordination and may improve reaching performance.

Progress Towards Specific Aims: A novel neck brace has been developed for the purposes of neck control relative to the trunk. This neck brace allows three directions of movement, which can provide forces to the head in specific directions. Testing of the brace confirmed its ability to position the head in accurately, and provide single-plane forces.

A seated reaching task was conducted with healthy subjects wherein the head and trunk coordination was analyzed. The posture of the head and trunk were collected and organized as a percentage of the overall reaching movement.

Impact: This project may improve the way patients with SCI perform seated reaching tasks. Insights gained from characterization can answer underlying questions about head-trunk coordination and rehabilitation in people with SCI.

**6. Icahn School of Medicine at Mount Sinai**

Ravi Iyengar, Ph.D.; Nicholas Johnson, Applicant Fellow
Postdoctoral: $191,978
Multi-Drug Combination Effects on Physical Therapy-Enabled Recovery After SCI

Introduction/Background: Spinal Cord Injury (SCI) is a debilitating disease that affects approximates 305,000 people in the United States. SCI involves the interruption of nervous connection between the brain and the body, leading to the loss of sensation and motor function. There are no approved pharmacological interventions for SCI, but physical therapy improves function in most patients. However, functional recovery is often limited. SCI is particularly intractable because central nervous system neurons, including the spinal cord, do not intrinsically regenerate. With SCI, neurons also face extrinsic inhibitors to regeneration. The Iyengar lab has identified drug targets to overcome both the intrinsic and extrinsic factors inhibiting functional recovery after SCI and has shown the efficacy of this drug combination in an optic nerve model of nerve injury. The goal of this project is to show the efficacy of this drug combination for improving functional outcomes in combination with physical therapy in an animal model of SCI.

Progress Towards Specific Aims: The Fellow, Nick Johnson, has completed pilot experiments with mice to identify an injury severity that recapitulates severe injury in humans, in which there will be a measurable difference between the natural recovery mice experience over this time period, the recovery with physical therapy, and the recovery with the full combination of physical therapy and pharmaceutical intervention.

The proposed experiments have begun. He has performed the surgeries necessary for intracranial injections and the first cohort of this experiment will be completed in the coming weeks.

Impact: By the end of this experiment, the research team will have shown the efficacy of a combinatorial therapy for SCI. By combining a pharmaceutical approach and physical therapy, they anticipate that animals will show 90% or more functional recovery over just 60% without intervention. Functional recovery is the most important goal in the treatment of SCI. This project is the next step in developing a treatment for humans that provides complete or near-complete functional recovery following SCI.

**7. Columbia University**

Sunil K. Agrawal, Ph.D.; Chawin Ophaswongse, Applicant Fellow
Postdoctoral: $180,000
Improving Trunk Control While Seated on Wheelchairs in Individuals with Spinal Cord Injury Using Robotics

Introduction/Background: Individuals with cervical or high thoracic spinal cord injuries (SCI) often rely on wheelchairs for mobility but face significant challenges in activities of daily living (ADL) due to impaired trunk control and stability. Tasks such as eating, working at a desk, opening doors, or reaching for objects can become difficult. While passive devices may provide trunk support in wheelchairs, they often restrict mobility and limit opportunities for postural rehabilitation. To address this, researchers have developed the Wheelchair for Active Postural Support System (WRAPS), an actuated robotic torso support system. WRAPS stabilizes the trunk while allowing controlled motion during seated activities, offering SCI patients the potential to improve their postural control and better assist with ADL.

Progress Towards Specific Aims: Specific Aim (I), (II): The BioRob2024 manuscript on postural coordination training using the pWRAPS in VR has been accepted for the conference. Researchers recruited 16 additional able-bodied subjects, bringing the total to 32, to investigate the effects of different Virtual Reality (VR) game feedback types in both unguided and guided conditions with the pWRAPS. The protocol for SCI patients has been developed and is currently under review by the Columbia Institutional Review Board (IRB). An overhead safety harness system has been installed in the experimental area to ensure the safety of SCI patients during the future experiment. Specific Aim (III): Preliminary data processing has been completed.

Impact: The accepted manuscript will be presented at the BioRob 2024 conference to disseminate the results of this research. Additionally, the first experiment with the pWRAPS system involving SCI patients will be conducted.

**8. Cornell University**

Yadong Wang, Ph.D.; Catia Dombaxe, Applicant Fellow
Predoctoral: $122,400
Examine the effects Goldfish Extracellular Matrix (ECM) Hydrogel and Chondroitinase ABC (ChABC) in Injured Mice.

Introduction/Background: Every year, half a million individuals worldwide face the devastating impact of Spinal Cord Injury (SCI), with 18,000 cases in the US alone. With no effective treatment currently available, the urgency to develop new therapies

is paramount. This research unveils a groundbreaking approach inspired by the regenerative capabilities of lower vertebrates, such as goldfish. The proposed treatment involves a Hyaluronic Acid blend hydrogel delivering naturally occurring regenerative proteins found in goldfish spinal cord (gECM) and stabilized Chondroitinase ABC (ChABC) in a lipocoacervate (ChABC-LipCo). This combination therapy aims to create a growth-permissive environment for axonal regrowth and inhibit scar tissue formation in mouse models of SCI.

Progress Towards Specific Aims: Researchers successful decellularized goldfish spinal cord tissue. The tissue harvested at 5 weeks timepoint was used to conduct proteomics and bioinformatics analysis. Through the bioinformatics analysis, researchers found the top 5 proteins with biological function in tissue regeneration, wound healing, and anti-inflammatory properties. Further analysis are being conducted to validate these proteins. Additionally, since the goldfish ECM does not form a hydrogel, researchers decided to test the goldfish ECM lyophilized powder in vitro using a dorsal root ganglion (DRG) explant mouse model. Premilinary results show extensive neurite outgrowth in treatment group compared to control group.

Impact: This research promises a paradigm shift in SCI treatment, offering hope to thousands. By harnessing nature's regenerative mechanisms and combining them in an innovative therapeutic approach, this study aims to provide a novel methodology for spinal cord regeneration in mice. The potential for a minimally invasive injectable treatment could significantly enhance patient care, allowing individuals to regain lost functions and improve their overall quality of life. This journey from nature's insights to transformative therapy holds the key to revitalizing hope for those affected by SCI worldwide.

**Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activates (IDEA) in Spinal Cord Injury Research (Round 4)**
**IDEA Contract Term 11/01/2021-10/31/2023; PART Contract Term 11/01/2021-10/31/2024**

**Progress Reporting Period**
**11/01/2021-10/31/2023 (IDEA); 11/01/2021-10/31/2024 (PART)**

**9 Awards, Procurement Total: $3,490,176**

1. **Research Foundation for SUNY Stony Brook**
   Michelino Puopolo, Ph.D.
   IDEA: $360,000
   Targeting CaV3.2 Calcium Channel to Treat Chronic Neuropathic Pain Following SCI

   Introduction/Background: The majority of people (up to 60-70%) leaving with spinal cord injury (SCI) develop chronic neuropathic pain. Hyperexcitability and spontaneous activity of nociceptors (pain-sensing neurons) are common to various neuropathic pain conditions, suggesting that a similar underlying mechanism(s) may also be responsible for the development of SCI-induced neuropathic pain (SCI-NP). The goal of this research project is to test the core hypothesis that the increased activity of CaV3.2 channels (the predominant isoform of T-type calcium channels expressed in nociceptors) induced by SCI drives SCI-nociceptors to a hyperexcitable state and promotes the development/maintenance of SCI-NP.

   Progress Towards Specific Aims: Researchers completed the behavioral experiments in vivo in female mice to determine the contribution of CaV3.2 channels to the development/maintenance of mechanical hypersensitivity and spontaneous pain following SCI. The numebr of animals included in the analysis was increased to a total of n=12 wild-type SCI and n=12 wild-type sham mice. The mechanical hypersensitivity was measured with the von Frey filaments. The data show that there is a significant drop in the mechanical threshold in the SCI mice but not in the sham mice. TTA-P2 (10 mg/kg, i.p.) reduced the mechanical hypersensitivity in SCI mice but not in the sham mice. Spontaneous pain was measured with the conditional place preference (CPP) paradigm. The data show that there is a significant shift towards the chamber paired with TTA-P2 (a selective blocker of CaV3 channels) in the SCI mice but not in the sham mice. Taken together with previous data in male mice, the completed set of data suggest a major contribution of CaV3.2 channels to the development/maintenance of chronic neuropathic pain following SCI both in male and female mice

   Impact: Identification of CaV3.2 as the principal ion channel responsible for driving SCI-nociceptors to a hyperexcitable state will provide a new pharmacological target to treat SCI-NP.

2. **Research foundation for SUNY Stony Brook**
   Irene C. Solomon, Ph.D.
   IDEA: $357,782
   Neuroprotective Strategies to Minimize SCI Tissue Damage and Improve Bladder and Respiratory Function

Introduction/Background: Spinal cord injury (SCI) initiates a secondary cascade of pathological processes that leads to further cellular/tissue damage and loss. Thus, there is a need to develop, implement, and optimize therapies focused on minimizing the extent of secondary injury-related cellular/tissue damage and loss following SCI. To this end, administration of the antibiotic minocycline (MIN) and the peroxisome proliferator-activated receptor gamma agonist pioglitazone (PIO), both of which are commonly used FDA-approved clinical agents, have been shown to exert neuroprotective actions in central nervous system injury/disease. The efficacy of these agents on bladder and respiratory dysfunction following SCI are unknown. Therefore, this project is designed to investigate the neuroprotective effects of MIN, PIO, and combined MIN/PIO treatment as a pharmacology-based therapeutic strategy to minimize secondary injury-related neural tissue damage/loss and promote improvement of bladder and respiratory function in an adult rat moderate contusion SCI model.

Progress Towards Specific Aims: Researchers have conducted additional data analysis for our experiments evaluating the effects of 7-day MIN (or baytril (BAY) control) treatment beginning at 24-hr post-SCI on reflex micturition behaviors in anesthetized rats. These analyses revealed that in ~67% of the rats treated with MIN at this time point post-SCI, in addition to the reduction in SCI-related bladder overactivity, a restoration of bladder-sphincter coordination was observed. Researchers have also continued processing of SCI tissue samples for evaluation of the lesion site, including MIN-induced changes in anti-inflammatory and neuroprotective markers. Researchers also restarted pilot experiments evaluating the effects of 7-day PIO (or PBS vehicle control) treatment following SCI on recovery of spontaneous and reflex bladder function; however, the data have not yet been analyzed.

Impact: The study is implementing a promising non-invasive pharmacology-based neuroprotective intervention strategy using currently available FDA-approved agents to minimize SCI-induced secondary injury-related neural tissue damage/loss and promote spontaneous improvement in bladder function in an adult rat moderate contusion SCI model. This therapeutic approach could be easily integrated into clinical use to facilitate recovery of bladder function and exert a significant positive impact on quality of life in SCI patients.

**3. The Trustees of Columbia University in the City of New York**
Sunil K. Agrawal, Ph.D.
IDEA: $346,220
Wheelchair Robot for Active Postural Support (WRAPS) of People with Spinal Cord Injury

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

Progress Towards Specific Aims: As a part of Specific Aim 1, Researchers have fabricated a robotic device for pelvic assistance on a wheelchair or pelvic Wheelchair Robot for Active Postural Support (pWRAPS). The robot has an in-parallel architecture with three rotational degrees-of-freedom (DOFs). The end-effector translation is coupled to the rotation to accommodate the natural movement of the pelvis on the seat. The device was tested with human subjects to evaluate how assistance by the brace to the pelvis can facilitate movements. Researchers have integrated a virtual reality (VR) system with WRAPS to evaluate human performance in different everyday reaching motions and evaluate the human performance while being assisted by WRAPS.
As a part of Specific Aim 2, Researchers have integrated a pressure mapping system under the seat of the user to characterize how the center of pressure (COP) under the buttocks changes during different maneuvers of the human body while sitting. This pressure map was further analyzed spatially and temporally during reaching movements. Also, algorithms were designed and are being currently tested for facilitating movements of the upper body to place the COP around as a way to mitigate excessive pressures under areas of the seat in people with spinal cord injury.

Impact: This is the first time a wheelchair robot with active postural support has been developed for wheelchair users, especially for those with spinal cord injury. pWRAPS will be investigated for assistance and training of upper body movements during functional tasks.

**4. Winifred Burke Medical Research Institute**
Yutaka Yoshida, Ph.D.
PART: $990,000
Novel Combinatorial Approach to Improve Motor Recovery After Spinal Cord Injury

Introduction/Background: Spinal cord injury (SCI) often causes permanent paralysis due to failure of injured corticospinal (CS) axons to regenerate. Since different strategies (e.g. blocking repellent extrinsic signaling, altering intrinsic signaling, modulating neuronal activity) have limited success to induce regeneration of injured CS axons and motor recovery after SCI. Thus, there is a critical need to combine different strategies to induce regeneration of injured CS axons and motor recovery after SCI.

The goal of this study is to develop a novel strategy to promote regeneration of corticospinal neurons (CSNs) and motor recovery after SCI. Our overall objectives of this application are to test the hypothesis that simultaneously 1) inhibiting axonal repellent, extrinsic signaling in CSNs, 2) modulating intrinsic signaling in CSNs, 3) inducing neuronal activity of CSNs as well as their target spinal INs after SCI will improve regeneration of injured CS axons, CS connectivity and motor recovery after the dorsal hemisection and contusion model of SCI at upper cervical levels.

The central hypothesis of this proposal is that the combined modulation of extrinsic and intrinsic signaling pathways together with neuronal stimulation of both cortical neurons and their target spinal interneurons will facilitate regeneration and connectivity of injured CS axons, and motor recovery after SCI. Determination of the combined

strategy after SCI in mice will provide new opportunities for development of novel therapy for SCI patients in humans.

Impact: At the completion of the proposed research, the expectation is that Researchers will determine whether their novel combined strategy by modulating both intrinsic and extrinsic signaling pathways and by activating neurons in the cortex and the spinal cord will promote axonal growth, connectivity, and motor recovery after SCI. These studies will have positive impacts to advance our mechanistic understanding of the synergistic effects using combined strategy after SCI, thereby providing knowledge which is essential to the future design of new interventional strategies to treat human SCI patients.

**Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activates (IDEA) in Spinal Cord Injury Research (Round 5)**
**IDEA Contract Term 10/01/2022-09/30/2024; PART Contract Term 10/01/2022-09/30/2025**

**Progress Reporting Period**
**10/01/2022-09/30/2024 (IDEA); 04/01/2024-09/30/2024 (PART)**

**9 Awards, Procurement Total: $5,682,568**

1. **Sloan Kettering Institute for Cancer Research**
   Dimitar B. Nikolov, Ph.D.
   IDEA: $360,000
   Promoting Neuronal Regeneration by Targeting the Alpha Secretase Cleavage of p75 With Monoclonal Antibodies

   Introduction/Background**:** Upon spinal cord injury, axons attempting to regenerate need to overcome the repulsive actions of myelin-associated inhibitors, including the myelin-associated glycoprotein, Nogo-A, and the oligodendrocyte myelin glycoprotein. These inhibitors bind and signal through a neuronal receptor/co-receptor/transducer complex comprised of NgR1, Lingo-1 and p75. Consequently, p75 is cleaved by alpha-secretase followed by gamma-secretase, triggering downstream signaling that inhibits axonal regrowth. ADAM10 and ADAM17 are both known to function as alpha secretases in neurons, however the interaction of p75 with ADAM's is yet to be studied. Researchers have previously shown that the ganglioside GT1b facilitates the assembly of the NgR1/Lingo-1/p75/Nogo-A/GT1b (5-component/5-mer) complex. Researchers have also now generated a panel of anti-ADAM monoclonal antibodies (mAbs) that disrupt the binding of ADAM's to substrates implicated both in cancer biology and in axon guidance. In this proposal, Researchers will investigate the potential of these mAbs to inhibit p75 cleavage upon spinal cord injury. Such an inhibition should impede the signaling pathway that prevents neuronal regeneration.

   Progress: Aim 1A Researchers have shown that ADAM17 binds to p75 only in the context of the neuronal receptor/co-receptor signaling complex, and that the binding is mediated by the D+C domain region of ADAM17. Aim 1B**:** Researchers have established protocols to purify the neuronal and neuron-myelin signaling complexes. Data collection and processing using cryoEM is underway. Aim 2A**:** Using cell-based neurite-outgrowth assays, Researchers have shown that the anti-ADAM17 mAbs block p75 cleavege and are highly potent in promoting regeneration upon neuronal injury. Aim 2B**:** Researchers have determined the cryo-EM structures of two different anti-ADAM17 mAbs bound to different domains of ADAM17.

   Impact: The novel therapeutic monoclonal antibodies characterized during this study could spur the development of new strategies for the treatment of spinal cord injury and paralysis.

2. **Winifred Masterson Burke Medical Research Institute**
   Edmund R. Hollis, Ph.D.; Kathleen M. Friel, Ph.D.
   PART: $990,000

Enhancing Nerve Transfer Surgery to Restore Hand and Arm Function in Chronic Tetraplegia

Introduction/Background: Individuals who have limited use of their arms and hands because of spinal cord injury (SCI) experience a decreased quality of life and incur significant long-term care costs. Approximately one-third of people with chronic SCI could benefit considerably from nerve transfer surgery, where working nerves are transferred to paralyzed arm muscles to restore movement. Although the procedure has the potential to greatly enhance arm function, outcomes can vary. The primary objective of this research is to improve recovery for these individuals by exploring two avenues that have the potential to enhance outcomes.

Progress Towards Specific Aims: Aim 1. Determine the effects of robot-assisted rehabilitation on dexterous hand movements and cortical motor map changes in tetraplegic individuals following nerve transfer surgery (Pilot Clinical Trial). The first aim of this study involves investigating whether robotic training of the arm that underwent nerve transfer can improve movement and strength recovery. Four participants were enrolled, three of whom have completed six weeks of robotic training at one-year post-surgery. An additional individual has had nerve transfer surgery and is currently undergoing robotic training.
Aim 2. Determine the regeneration-promoting effects of conditioning electrical stimulation in a large animal model of radial nerve repair. All four subjects have completed behavioral and electrophysiology studies and researchers are currently performing histological studies. Evaluation of behavioral outcomes and histology is ongoing.

Impact: The planned research will provide crucial insights into how to optimize outcomes for individuals with SCI who undergo nerve transfer surgery.

**3. Research Foundation for SUNY Stony Brook**
Irene C. Solomon, Ph.D.; Steven J. Weissbart, M.D.
PART: $986,610
Therapeutic Intermittent Hypoxia to Reduce Detrusor Overactivity and Symptom Severity in Chronic Incomplete SCI: Translation and Mechanisms

Introduction/Background: Spinal cord injury (SCI) has a profound negative impact on lower urinary tract (LUT) function, resulting in problems with urine storage and emptying of the bladder that are associated with a high degree of morbidity and a poor quality of life. While the injured spinal cord exhibits a robust capacity for neural plasticity that promotes spontaneous functional recovery, this recovery is rarely complete, and deficits persist. Preclinical studies in our laboratory have been using neural plasticity-inducing acute intermittent hypoxia (AIH) as a strategy to reduce bladder over-activity (*i.e.*, non-voiding bladder contractions) and promote improvements in bladder function in rats with SCI. While the researchers observations are encouraging, the impact of therapeutic AIH as a strategy to improve bladder function in humans with SCI remains to be evaluated. Moreover, the neural mechanisms that underlie AIH-induced improvements in bladder function are unknown. This project is designed to initiate translation of our work (SA1: human subjects - *proof of concept pilot study*) and evaluate possible neural mechanisms for AIH-induced improvements in LUT function (SA2: preclinical rat studies).

Progress Towards Specific Aims: Researchers have continued with recruitment for the SA1 experiments evaluating the effects AIH treatment on clinical indices of LUT function in human subjects with neurogenic bladder (SCI and MS). Researchers have also continued with SA2A experiments evaluating potential contributions of serotonergic (5-HT) mechanisms in AIH-induced improvements in LUT function.

Impact: This project will provide novel information about the benefits of AIH therapies to improve clinical indices of bladder function and symptom severity/bother in SCI, identify potential neuromodulatory mechanisms (which have yet to be determined in SCI) that contribute to AIH therapy-induced improvements in bladder function in SCI, and lay the groundwork to enable future clinical trials and the transition of AIH therapies to clinical management of bladder dysfunction following SCI.

4. **Winifred Masterson Burke Medical Research Institute DBA Burke Neurological Institute**

Vibhu V. Sahni, Ph.D.
IDEA: $360,000
Mechanisms Controlling Early and Segmentally Distinct Loss of Long-Distance Corticospinal Axon Regenerative Ability

Introduction/Background: Regenerating the damaged connections between the cortex and the spinal cord is a major goal for functional recovery after spinal cord injury (SCI) in humans. These connections form the corticospinal tract (CST), which is the principal circuit responsible for voluntary control in humans. Damage to this circuit following SCI is a major cause for the loss of motor ability. Numerous efforts have therefore aimed at CST regeneration after SCI to enhance functional recovery.

Several investigations have previously established that there is a decline in CST regenerative ability from development into adulthood. Multiple lines of experiments have found that when this tract is damaged in young animals, there is greater plasticity and regeneration when compared to the similar injuries in adult animals. Several molecules have been identified that control this decline in regenerative ability from development into adulthood. However, manipulation of these molecules has only produced limited CST regeneration after adult SCI. Further, the CST regeneration that is observed following these experimental manipulations only occurs for a short distance beyond the injury site; long-distance CST regeneration remains an unattained goal. This suggests that there are additional molecules, yet to be identified, that can contribute toward this long distance CST regeneration.

Summary of goals and objectives: In work previously funded by the SCIRB researchers developed a new model of experimental CST injury in mouse pups. Through this work, researchers identified that long distance CST regenerative ability is lost much earlier in development than previously believed, i.e. this loss of regenerative ability is even seen when the CST is lesioned in mouse pups. Researchers therefore propose to build on these surprising results and investigate the developing nervous system to identify the molecules that contribute to this early loss of regeneration. Researchers propose to use new genetically engineered mouse lines, in combination with our new model of experimental CST injury, as well as gene profiling approaches and advanced bioinformatic analyses to identify new molecules that limit CST regeneration during early development. Researchers will analyze both,

the neurons that originate the CST, as well as the developing spinal cord at specific levels, for this purpose.

Progress Towards Specific Aims: Researchers have made substantial progress in both Aims 1 and 2. In our previous report, researchers had described that were establishing the protocol to use single nuclear sequencing to investigate the molecular profiles of CSN in response to microsurgical SCI. To this end, in Aim 1, researchers had collected CSN nuclei from control non-lesioned mice. Our next step was to use this approach to compare the responses of developing CSN to microsurgical SCI. Researchers have run this experiment and isolated both, control CSN (retrogradely labeled from cervical C2) and CSN that were axotomized at cervical C2 at P4. This latter lesion abolishes long-distance CST regeneration during development. While analyses are ongoing, our results are that the microlesion does not disrupt CSN molecular profiles. This intriguingly suggests that an axotomy of developing CSN does not alter the molecular program of CSN development and differentiation. In Aim 2, to identify extrinsic regulators in the spinal cord that control long distance, CST regenerative ability, researchers had begun to use a new bioinformatics protocol to probe our RNAseq data sets for potentially novel regulators of this process using principal component analysis. Researchers have now used this to perform a “removal of unwanted variables” method to force clustering of RNA samples from the lesioned cord into groups depending on their ability to foster long-distance axon regeneration. Using gene ontology analyses, researchers have identified axon guidance mechanisms as the only mechanism that distinguishes these groups implicating these mechanisms as the potential “missing link” in our attempts to reinstate long-distance CST regeneration after adult SCI.

Impact: This work will have significant impact because the developing nervous system has never been previously investigated in the context of loss of long-distance CST regeneration ability, since regeneration was believed to be intact at this time. Our experiments will identify cells and molecules that control long-distance CST regeneration, a presently unattained goal in regenerative neuroscience. Further, this work will provide for the field, large scale datasets that can be mined for additional molecules for directing CST regeneration at distinct spinal levels. The hope is that these new molecules could provide the “missing links” that could eventually be utilized in combination with established approaches to promote CST regeneration after adult SCI.

**5. Icahn School of Medicine at Mount Sinai**
Leif A. Havton, M.D., Ph.D.
PART: $926,620
Augmentation of Bladder Function by Transcutaneous Spinal Cord Stimulation After Conus Medullaris Injury in Primates

Introduction/Background: Injuries to the most caudal portion of the spinal cord, including the sacral segments of the spinal cord are referred to as conus medullaris (CM) forms of spinal cord injury (SCI). Associated lumbosacral nerve roots, referred to as the cauda equina (CE), are typically also injured in the setting of trauma to the lower thoracic and upper lumbar spine. The overall goal for this is to explore the potential utility of non-invasive transcutaneous spinal cord stimulation (TSCS) for improving bladder emptying after a CM/CE form of spinal cord injury. The studies are performed in a non-human primate (NHP) model of an incomplete CM/CE form of SCI. An incomplete avulsion injury to ventral roots that innervate the lower urinary tract is

performed in male and female rhesus macaques with the goal of achieving an LUT denervation of approximately 50%. At multiple time points after the injury for a post-operative study period of 6 months, physiologic studies of the lower urinary tract, including urodynamic bladder pressure recordings during bladder filling and emptying, are combined with transcutaneous spinal cord stimulation in NHPs under light sedation. The partial filling of the bladder is performed to activate voiding reflexes in sedated Voiding and efficiency of bladder emptying information are collected both with and without TSCS.

Progress Towards Specific Aims: During the first reporting period work was performed to meet the institutional requirement for the proposed animal studies at the California National Primate Research Center (CNPRC)/UC Davis. This included the preparation of the UC Davis Institutional Animal Care and Use Committee (IACUC) protocol for NHP research studies and assignment of training to research team members based on UC Davis training requirements for work with NHPs.

Impact: Studies of conus medullaris (CM)/cauda equina (CE) forms of spinal cord injury represent an underserved area of basic and translational research. Presently, there are no available treatments to reverse or augment neurological functions after CM/CE injuries in patient populations. If successful, planned studies may contribute to the development of a new neuromodulation treatment strategy, using non-invasive electrical stimulation of the spinal cord, to augment voiding and bladder emptying after CM/CE injuries. Improved bladder function after spinal cord injury has been recognized by several patient groups as a high priority for improved quality of life and independence in the community.

**6. Albany Research Institute, Inc.**
Disha Gupta, Ph.D.
IDEA: $356,538
Operant Conditioning of Somatosensory Evoked Potentials to Improve Motor Function after SCI

Introduction/Background: This study aims to improve functional recovery in individuals with incomplete spinal cord injury (iSCI) by enhancing weakened central nervous system responses to sensory input. While most rehabilitation research focuses on restoring motor control through descending pathways, sensory impairments—often overlooked—play a crucial role in motor function. Sensory input is essential for effective movement, and its loss can limit motor rehabilitation. This study utilizes Targeted Neuroplasticity via a novel non-invasive Brain-Computer Interface (BCI) to strengthen sensory pathways and support overall recovery.

Progress Towards Specific Aims: This study has two aims: i) To develop and validate a novel somatosensory BCI that uses operant conditioning to augment the sensory brain response; ii) Assess its impact on behavioral function and physiology. The sensory BCI system called Cortical-Evoked Potential Operant Conditioning System (C-EPOCS) has been developed and tested to support conditioning of both upper and lower limbs. Vibrotactile (sensory) and robotic (motor) assessment protocols for longitudinal testing have been optimized, including testing their inter-session reliability.

Impact: This study has resulted in the development of a) C-EPOCS–a BCI that enables realtime operant conditioning of a targeted brain response. Built upon the foundation of EPOCS—a system currently structured for processing muscle responses—C-EPOCS enables real-time processing and feedback of sensory brain responses. It supports pseudo-real-time data analysis and rapid target threshold selection; b) optimized stimulation protocol and analysis pipeline designed to reliably elicit target somatosensory cortical components, with inter-session stability; c) programmable trigger hardware, (useful for various neuroscience studies); d) vibrotactile sensory assessment system including open-source vibrotactile hardware assessment software; d) integration of neurophysiological assessment system with a robot-based kinematic evaluation system.

**7. The Research Foundation of CUNY obo City College of New York**
Ashiwel S. Undieh, Ph.D.
IDEA: $360,000
Nucleolipid Signaling for Spinal Cord Regeneration

Introduction/Background: Brain-derived neurotrophic factor (BDNF) is an endogenous growth factor that promotes nerve cell resilience and regeneration following injury. When BDNF initiates cell signaling by stimulating its TrkB receptors, the first step in the downstream cascades that produce the desired responses is the conversion of phosphatidylinositide from inactive PIP2 to activated PIP3. In lab experiments where BDNF availability to the receptor can be increased at will, it is known that the greater the BDNF concntration, the greater the stimulation of BDNF's TrkB receptors, and the greater the PIP3 response. As such, one could consider boosting BDNF levels as a therapeutic strategy. However, multiple attempts have shown that BDNF itsel is not a good drug candidate, partly because when injected into the blood stream the protein cannot diffuse into the spinal cord sites where injury occurs. An alternative strategy derives from the observation that the availability of PIP2 also determines the PIP3 response: the higher the amounts of PIP2 available to TrkB, the more robust will be the production of PIP3 in response to receptor stimulation. To restore or increase the availability of PIP2, the cell must first make its precursor, the nucleolipid CDP-diacylglycerol (CDP-DG). The goal of the studies is to discover and characterize the drug-like properties of compounds that can promote BDNF signaling by increasing the biosynthesis of CDP-DG thereby boosting the supply of PIP2 to enhance TrkB receptor signaling. Such drugs could promote neuroprotection and neuroregeneration by amplifying TrkB signals and downstream support of nerve cell function and resilience.

Progress Towards Specific Aims: Researchers studied 24+ structural and pharmacologic analogs of our prototype compound, SKF38393, for effects on CDP-diacylglycerol induction in brain slice preparations, and tested a selection of effective nucleolipid-inducing compounds in the neuronal regeneration assay. Researchers also tested several compounds known to promote neuronal regrowth or sprouting but which may not induce CDP-DG. Thirdly, researchers tested for effects of synthetic CDP-diacylglycerol on neuronal regrowth. The experimental objectives under Aim #1 have been achieved. Although the project period has ended, data analysis will continue in order to finalize the results for publication.

The gait data obtained from the Noldus Catwalk system is comprised of some 28 variables that probe various gait components for left and right forelimbs versus left and right hindlimbs. While a preliminary analysis shows some of the variables to be

significantly different among the drug treatment groups, researchers are continuing to examine the data to understand the relationships among the collected variables before making conclusive deductions.

Impact: Development of combinatorial neuromodulation strategies to boost brain to muscle response plasticity for corticospinal tract connectivity will open new directions for biological therapies for SCI. With these studies, researchers expanded their "neuromodulation toolbox" of preclinical therapies. If effective, the invasive chemogenetic neural activation approach may may be implemented non-invasively in humans using non-invasive transcranial direct current stimulation (tDCS) and pharmacological approaches. Epidural TBS stimulation, which is minimally invasive, could be replaced with non-invasive TMS.

8. **The Research Foundation of CUNY obo City College of New York**
John Martin, Ph.D.
PART: $982,800
Leveraging LTP to Promote CST Axon Sprouting in the Spinal Cord

Introduction/Background: Restoring function after SCI will depend on durable plasticity to reconnect the brain, where movements are initiated, with the spinal cord below the cervical injury, where most distal arm movements are produced. Promoting reconnection through and beyond the injury currently is not yet possible. However, since most SCIs are incomplete, spared connections below the injury are an important therapy target to make spared connections more abundant and stronger. This project focuses on the corticospinal tract (CST), which is the brain circuit essential for skilled movements. Our published studies show that a neuromodulatory approach called theta burst stimulation (TBS) enhances activity-dependent CST axon sprouting and synaptogenesis. TBS also induces long-term potentiation (LTP) in the corticospinal motor system. In this project, researchers continue to study a potential link between muscle response LTP and CST axon growth with the aim of enhancing CST axon outgrowth after SCI to promote function. In Aim 1, researchers enhance motor cortex LTP to grow new CST connections in healthy rats, and in Aim 2, after cervical contusion injury. Aim 3 investigates translation from electrical neuromodulation to promote CST connections to using transcranial magnetic stimulation (TMS).

Progress Towards Specific Aims: Researchers observe that the combinatorial approach not only boosts axon growth, resulting in a 6-fold increase in CST density within the cervical spinal gray matter intermediate zone compared with sham controls, but leads to extensive growth in the gray matter region where motor neurons are located. There, researchers see formation of putative synaptic connections with motor neurons, suggesting a functional connection. Researchers do not yet observe that the combined approach boosts muscle response plasticity beyond that observed with TBS alone. For Aim 3 experiments, researchers have completed the mathematical modeling estimating the electrical field induced by magnetic stimulation. Researchers also created a model for epidural electrical stimulation. Compared with the field produced by epidural electrical stimulation at a current when a motor response is produced, the field induced by TMS is both broader and less intense at levels producing similar motor effects. The modeling results show promise for translation of the electrical TBS to the human using magnetic stimulation.

Impact: Development of combinatorial neuromodulation strategies to boost brain to muscle response plasticity for corticospinal tract connectivity will open new directions for biological therapies for SCI. With these studies, researchers expanded their “neuromodulation toolbox” of preclinical therapies. If effective, the invasive chemogenetic neural activation approach may may be implemented non-invasively in humans using non-invasive transcranial direct current stimulation (tDCS) and pharmacological approaches. Epidural TBS stimulation, which is minimally invasive, could be replaced with non-invasive TMS.

**9. Winifred Masterson Burke Medical Research Institute**
Edmund R. Hollis, Ph.D.
IDEA: $360,000
Role of SPARC in Pathological Wound Healing After SCI

Introduction/Background: This study aims to determine the role of the Secreted Protein Acidic and Cysteine Rich (SPARC) protein in wound healing after spinal cord injury (SCI). Previous evidence demonstrates that SPARC is a key regulator of collagen deposition and fibrosis in non-neural tissues, and the proposed research investigates the effects of SPARC deletion on scar formation and functional impairment in neural tissue in a rodent model of SCI.

Progress Towards Specific Aims: The first specific aim is to characterize the temporal and spatial expression profile of SPARC after SCI. Researchers found that SPARC expression increases in astrocytes shortly after SCI and that SPARC expression is maintained until the late remodeling phase (30 days after SCI). The second aim is to determine the effect of SPARC deletion on scar formation and functional impairment after SCI. Using a *SPARC*-null mouse line, researchers have found that the loss of SPARC results larger lesion volumes and impaired motor recovery after spinal cord injury. Reactive astrogliosis and wound healing are disrupted in the *SPARC*-null mice. Furthermore, the growth-inhibitory fibrotic core of the lesion is increased following SPARC deletion. Researchers found that SPARC deletion affects astrocyte cellular remodeling but not microglia cellular remodeling after injury.

Impact: The contribution of this proposed research is that researchers expect to determine the role of SPARC in regulating fibrosis and scarring after SCI. This contribution will be significant because it is expected to define the role of a key driver of non-neural tissue fibrosis in the context of SCI, connecting the fields of non-neural and neural wound healing. The accessibility of non-neural tissues, such as epithelial tissues, has allowed for a rich characterization of the cellular and molecular mechanisms underlying non-neural wound healing. This represents a promising source of knowledge for identifying candidate approaches to alter SCI progression, enhance remodeling, and limit pathological scarring. Their proposed studies explore wound healing mechanisms after SCI through analysis of molecular effectors, cellular interactions, and structural changes. This represents an important step towards building an integrative knowledge base to advance the study of both acute and chronic SCI.

**Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activates (IDEA) in Spinal Cord Injury Research (Round 6)**
**IDEA Contract Term 10/01/2023-09/30/2025; PART Contract Term 10/01/2023-09/30/2026**

**Progress Reporting Period**
**04/01/2024-09/30/2024**

**8 Awards, Procurement Total: $5,275,108**

1. **Icahn School of Medicine at Mount Sinai**
   Thomas Bryce, M.D.
   PART: $910,611
   Biomarkers of SCI Pain Evolution During Acute Rehabilitation (BioSPEAR)

   Introduction/Background: Pain is common following spinal cord injury (SCI) and is an important factor affecting quality of life. Nearly all pain after SCI can be classified into either neuropathic (nerve) pain or nociceptive pain. Researchers are still working to understand more about how this pain develops, what predicts its onset, and the biology underlying the pain. The purpose of this research study is to document the experience of pain after SCI, its development and persistence early after injury during acute inpatient rehabilitation (AIR), a period when pain after SCI often develops; to identify a molecular biomarkers of neuropathic pain using hypothesis-driven and unbiased approaches; and to explore the relationships of biomarkers, clinical characteristics, and psychosocial factors present during AIR to the persistence of pain six months post-injury.

   Impact: The data gathered in this study are essential for designing studies to test future interventions aimed to prevent development of neuropathic pain, and to determine how current standard-of care interventions (pharmacological or non-pharmacological) may affect the establishment and trajectory of the pain. If successful, the findings from this study could lead to better, more personalized pain management strategies and could be tested further in larger clinical trials. This could ultimately change how researchers treat neuropathic pain following SCI, making the treatments more effective and less harmful. This could also help us better predict and manage pain in people recovering from SCI, potentially leading to more effective treatments and improved outcomes.

2. **Winifred Masterson Burke Medical Research Institute**
   Edmund Hollis, Ph.D.
   PART: $988,622
   Ephrin-Mediated Cortical Motor Circuit Rewiring

   Introduction/Background: This proposal aims to understand how rewiring motor circuits in the brain can improve movement recovery after spinal cord injury. The research will explore how reducing signals that repel axons helps reshape these motor circuits, promoting the recovery of function. The study will focus on how rewiring surviving circuits supports recovery, using advanced genetic and optical imaging to track changes in the brain's motor networks. To assess the role of specific areas in the network, certain circuits will be selectively shut off or removed. This research could provide insights into how circuit flexibility aids recovery, potentially leading to new treatments for spinal cord injury and stroke.

Progress Towards Specific Aims: Aim 1. Determine the structural plasticity of rewired corticofugal circuits induced by EphA4 deletion. The first aim tests the hypothesis that conditional deletion of the repulsive axon guidance receptor EphA4 will enhance axon sprouting of cortical projecting neurons after a unilateral corticospinal injury. Researchers have made significant progress on this aim, with EphA4 deletion driving robust axon plasticity across the midline in both the brainstem and spinal cord.
Aim 2. Record the activity changes in corticospinal neurons induced by EphA4 deletion. In this aim, researchers are testing the hypothesis that the formation of novel circuits will alter the activity of those cortical neurons that exhibit increased growth. In this period, researchers have recorded activity from four mice.
Aim 3. Identify the functional contribution of rewired corticospinal circuits induced by EphA4 deletion. In aim 3, researchers are testing the contribution of rewired circuits to the improved functional recovery that researchers observe with deletion of repulsive EphA4. In this period, researchers have tested and validated the targeting of brainstem motor circuits with a method for viral-mediated neuron ablation.

Impact: The planned research will provide critical insight into the extent to which axonal growth of motor circuits can drive widespread changes and provide a target for therapeutic intervention after spinal cord injury and stroke

**3. Icahn School of Medicine at Mount Sinai**
Hongyan (Jenny) Zou, M.D., Ph.D.
IDEA: $360,000
Investigate Glial Communication in Neural Repair After SCI

Introduction/Background: Glial communication is critical for injury resolution and wound compaction after spinal cord injury (SCI). Reactive astrocytes respond to SCI by extending long processes to form a protective barrier to seal the wound and provide a growth promoting glial bridge across lesion site. However, the molecular mechanisms governing astrocyte mobilization are not well understood. This proposal studies a novel role of axon guidance receptor Plexin-B1 in orchestrating astrocyte cell alignment for wound compaction and neural repair after SCI.

Progress Towards Specific Aims: Researchers conducted new live cell imaging coupled with advanced fluorescent probes to visualize membrane dynamics in reactive astrocytes. Researchers identified a novel role of Plexin-B1 in safeguarding long processes of reactive astrocytes from physical damage. Researchers uncovered a previously unappreciated role of membrane turnover governed by guidance receptor Plexin-B1 that enabled astrocytes to dynamically withdraw processes and engage contact inhibition of locomotion (CIL). These data provided new insight into how cells protect long processes without physical damage and how this is critical for cell-cell physical contact to resolve collision.

Researchers performed in vivo SCI studies showing that Plexin-B1 deficient astrocytes displayed increased aggregation and misalignment when encountering regenerating axons. This leads to larger lesion size, inflammatory spill over and glial disorganization, affecting functional recovery.

Researchers have submitted a manuscript reporting these exciting results, which was positively reviewed in *Nature Neuroscience*, with *acknowledgement of NYS SCIRB.* The editor at Nature Neuroscience has invited us for submit revision.

Impact: This study provides new cellular and molecular mechanisms of glial communication, in particular physical interaction and cell mechanics during wound healing and glial barrier after SCI.

**4. Winifred Masterson Burke Medical Research Institute**
Vibhu Sahni, Ph.D.
IDEA: $360,000
Structural Plasticity of Cortico-Brainstem Projections After SCI and Their Contributions to Functional Recovery

Introduction/Background: Spinal cord injury (SCI) damages direct connections between the cortex and the spinal cord causing paralysis. Some plasticity of these connections can mediate limited recovery after SCI. However, undamaged circuits can also exhibit plasticity, and this represents another resource for enhancing recovery after SCI. The cortex also directly communicates with the brainstem, a critical movement control center that also communicates directly with the spinal cord. Therefore, this cortex-brainstem-spinal pathway represents another way for the cortex to communicate with the spinal cord after SCI. However, due to technical limitations in the field, whether there is plasticity in the connections between the cortex and the brainstem after SCI remains an unanswered question. Further, the contribution of these connections to functional recovery after SCI remains completely unknown.

Several indirect lines of investigation have previously established that plasticity of the connections between the cortex and the brainstem can contribute toward recovery after cortical damage in stroke. However, to date a major limitation in investigating these connections has been that there have been no molecular tools that can specifically distinguish these nerve cells in the cortex from other cells that project to the spinal cord. Therefore, to date, it has not been possible to specifically identify and manipulate these nerve cells to interrogate these critical motor control connections. Evidence suggests that these connections will play a critical role in recovery after SCI. The project hopes to establish the foundation for addressing this critical question in the field of recovery after SCI.

Progress Towards Specific Aims: Researchers had previously reported obtaining a new mouse line – Cartpt-IRES-Cre mice. Using Cartpt-IRES-Cre mice, researchers had established that Cartpt+ neurons are CSN. Researchers had next proposed to obtain an Npy-FlpO mouse line in which Npy+ CBN would express FlpO recombinase. The plan was that by crossing these mice with Cartpt-IRES-Cre mice, researchers could then investigate the axonal projections of both Npy+ CBN and Cartpt+ CSN in the same mice. Researchers have obtained Npy-FlpO mice and have performed these experiments. Researchers have performed conditional retrograde and anterograde tracing experiments, which have now conclusively established and confirmed that Npy+ and Cartpt+ SCPN 1) are two distinct subpopulations, 2) reside in lateral sensorimotor cortex; and 3) extend distinct axonal projections wherein Npy+ CBN largely terminate their axonal projections within the rostral pons, while Cartpt+ CSN project axons to the cervical cord.

Impact: Researchers expect their experiments will unequivocally identify the role of cortico brainstem connections in SCI recovery, which will have direct impact on future neurorehabilitation approaches for SCI. The hope is that these could eventually be utilized in combination with established approaches to promote motor recovery after SCI. The brainstem also plays an important function in bowel and bladder function.

Therefore, these investigations and tools could also be manipulated to improve bowel and bladder function, an important goal for individuals living with SCI.

**5. Bronx Veterans Medical Research Foundation**
Noam Harel, M.D., Ph.D.
PART: $946,581
Optimizing Spinal Cord Associative Plasticity to Enhance Response to Hand Training in Cervical SCI

Introduction/Background: This project builds upon prior work to pair brain and spinal cord stimulation to strengthen nerve circuits controlling weakened hand muscles after spinal cord injury (SCI). Researchers hope to expand on this "Spinal Cord Associative Plasticity" (SCAP) approach by spending more time with each participant to individually optimize every aspect of the SCAP protocol, including combining SCAP with hand rehabilitation exercises. Researchers expect that SCAP will induce plasticity, whereas hand exercises will shape that plasticity into improved function.

Progress Towards Specific Aims: During the reporting period, two participants were enrolled in the study (of a planned 12). The initial year of enrollment was expected to be slow, partly due to the NYS grant being backdated by two months, the necessary start-up period, and because Researchers have focused on one active participant at a time at the beginning of this highly individualized project. One participant withdrew from the study. The other is nearly six months into his expected 9-10-month involvement.

Impact: Regaining control over hand function represents the top priority for individuals with cervical SCI. Furthermore, this approach could be compatible with other future interventions, including medications and cell-based treatments.

**6. University of Rochester**
Bradford C. Berk, M.D., Ph.D.
IDEA: $359,294
PDE10A Treatment for Neuropathic Pain After SCI

Progress Towards Specific Aims: Spinal cord injury (SCI) was generated by a contusion injury in all mice shown. Mice treated with MP-10 are labeled MP-10, while vehicle only treated mice are labeled Control. Mice treated with MP-10 compared to vehicle only showed a decrease in the expression of activated microglia (Iba1), leukocytes (CD45), reactive astrocytes (GFAP), endothelial cells (EC) involved in inflammation (ICAM-1), damaged neurons (NFH), and proliferating cells (Ki67). In contrast, intact neurons (NeuN) were increased by MP-10.

**7. Winifred Masterson Burke Medical Research Institute**
Edmund Hollis, Ph.D.
IDEA: $360,000
The Contribution of Wallerian Degeneration to Neural Tissue Inflammation and Axon Regeneration

Introduction/Background: Following traumatic injury to the central nervous system (brain, spinal cord, or optic nerve), the regeneration of damaged neural tissue is severely limited, resulting in permanent functional deficits. Mature nerve cells in

mammals are equipped with long, cable-like structures (called axons) that facilitate rapid transmission of electrical impulses among distant groups of cells. Injury to these cables disrupts communication lines, leads to their disintegration, and triggers an inflammatory response.

Progress Towards Specific Aims: In this study, researchers utilize transgenic mice in which the disintegration of transected axons does not result in destruction. Although axons are still severed, they remain stable for weeks after injury, enabling us to investigate whether the destruction of axons influences the neural repair response. Specifically, researchers employ experimental manipulations known to promote limited neural repair and examine whether this repair response is enhanced or diminished when injured axons resist disintegration. Preliminary studies have shown increased anatomical regeneration of axons following injury in transgenic mice. Researchers have begun spinal cord injury experiments outlined in Aim 2.

Impact: The proposed studies will be impactful because they will explore whether treatments aimed at protecting axons might hinder efforts to promote axon regrowth after spinal cord injuries. This research is important because it will uncover new insights into how the immune system responds to damaged axons in the injured spinal cord. Researchers anticipate that by completing this research, Researchers will better understand how the immune response is altered in the injured spinal cord when axon degeneration is impaired in mice. This will help us grasp how this degeneration affects the injured spinal cord and its role in the regrowth of spinal cord axons. These discoveries will lay the groundwork for developing therapies that focus on safeguarding axons after traumatic spinal cord injuries.

**8. Bronx Veterans Medical Research Foundation**
Welping Qin, M.D., Ph.D.
PART: $990,000
Novel Targeting Nanotherapeutics for Functional Recovery After Acute SCI

Introduction/Background: The goal of this reporting period is to synthesize the needed nanoparticles and to ensure each of these parameters meets the biochemical requirements for achieving proper biological functions for the funded study.

Progress Towards Specific Aims: Working together, researchers at the Bronx VA and Dr. Dong Wang's team at University of Nebraska Medical Center, have completed the synthesis of 9 different nanoparticles that are needed for the Aim 1 study. Each of these parameters meets the biochemical requirements that ensure to achieve proper biological functions for the funded study. Researchers are currently preparing the animal work for the proposed study.

In parallel, researchers published two manuscripts related to the project funded by NYS SCIRB.

Impact: The progress made over the reporting period will allow researchers to move the study toward the next phase.

## Translational Research Projects in Spinal Cord Injury (Round 4)
**Contract Term 10/01/2022-09/30/2027**

**Progress Reporting Period**
**04/01/2024-09/30/2024**

**2 Awards, Procurement Total: $7,566,394**

1. **The Feinstein Institute for Medical Research**
   Chad Bouton, M.S.
   $3,570,469
   Constant and Cortically Modulated Transcutaneous Spinal Cord Stimulation for the Treatment of Upper Extremity Impairment

   Introduction/Background: Spinal cord injuries can cause complete or partial paralysis by disrupting the flow of information between various parts of the nervous system, making it challenging for individuals to perform daily activities and achieve independence. The team has been researching transcutaneous spinal cord stimulation (tSCS) combined with activity-based training as an effective treatment for individuals with tetraplegia. In severe cases, additional methods are needed; our team developed a brain-computer interface (BCI) by utilizing multiple chips implanted in the brain's movement area to record and decode detailed information about movement-related activity.

   To that, researchers aim to restore arm/hand function in individuals with tetraplegia by using tSCS and a BCI. The combination of these two methods can promote changes in affected pathways and restore short-term and potentially long-term muscle control. Their study will involve participants who will receive tSCS only and participants who will receive tSCS followed by 6 months of BCI-driven tSCS.

   Progress Towards Specific Aims: Two participants have been enrolled into the study, one for each Aim. The participant for Aim 1 has begun their baseline period data collection. Researchers have been conducting calls with potential candidates for the additional slots related to Aim 1, and several candidates have visited the lab for further assessments of eligibility for the study as well. For Aim 2, one participant was successfully implanted with 5 microelectrode arrays in the motor and sensory cortices (per protocol) in March 2023 and has fully recovered from the procedure. This participant has been undergoing BCI testing, tSCS mapping, baseline sessions, and other tasks in preparation of BCI-mediated tSCS to promote recovery of upper extremity movement.

   Impact: Successful implementation of this treatment could significantly improve the quality of life by restoring arm/hand function to allow performance of activities of daily living, thereby increasing their independence.

2. **The Trustees of Columbia University in the city of New York**
   Sunil K. Agrawal, Ph. D.
   $3,995,925
   Improving Balance After Spinal Cord Injury Using a Robotic Upright Stand Trainer

Introduction/Background: People with SCI show balance deficits during upright standing and walking. It has been shown that neurorehabilitation is effective in incomplete SCI. However, the rehabilitation is challenging as the subjects have difficulty maintaining a standing posture without external support. Hence, the SCI rehab is personnel intensive and physically demanding. There is also a lack of standardized training protocols, and the training is performed over many sessions. It begs the question if one can make individual training sessions more efficient and effective. Our translational proposal is significant because researchers address all the above challenges using a novel robotic upright stand trainer (RobUST) that researchers have designed and tested at Columbia University. Our preliminary studies with mild and severe spinal cord injury patients show long-term changes in posture and balance in SCI due to training with RobUST. The specific aims as listed in the proposal are:

Aim 1. To improve training effectiveness of RobUST: (i) expand 2-dimensional planar programmed force-fields into 3-dimensions so that RobUST can train postural control in the horizontal plane while additionally providing body-weight support in the vertical plane to free up therapists; (ii) add virtual reality within RobUST so that users can perform simulated functional tasks that are physics-based, repeatable, and more motor engaging.

Aim 2. To characterize postural standing control mechanisms, both kinematic and neuromuscular responses, in participants with mild and moderate SCI across three postural control settings: i) standing with handlebar support, ii) standing with handlebar support and assistive force field, and iii) standing with force field.

Aim 3. To investigate postural-related functional improvements with RobUST-training in participants with mild and moderate SCI.

Progress Towards Specific Aims: The first year of the project focused on improving the different features within the RobUST robotic stand trainer system, e.g., (i) ability to apply multi-directional forces on the pelvis and the trunk, (ii) integrate virtual reality within RobUST for human interaction and training, (iii) characterize the trunk-pelvis coordination while standing during functional movements. The feasibility of these concepts was demonstrated and verified through human studies. These are summarized in some papers that were published (or have been submitted for publication). Please see the list below. Researchers were also able to publish the results of the joint work of our team at Columbia University and Dr. Rejc/Dr. Harkema's work with spinal cord injured patients.

Impact: SCI rehab is personnel intensive and physically demanding. Due to heterogeneity of the injury and subject-specific rehabilitation needs, there is poor scientific understanding and lack of standardized training protocols to affect outcomes. Additionally, the SCI posture training typically are long, up to 80 sessions, and expensive. This raises the question if there are ways to systematically decrease the number of training sessions by making individual sessions more efficient and effective. Researchers believe that our translational proposal is significant because this is the first research that is targeted to address all of the above challenges.

*Appendix III*

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2 Service Concluded During 2024