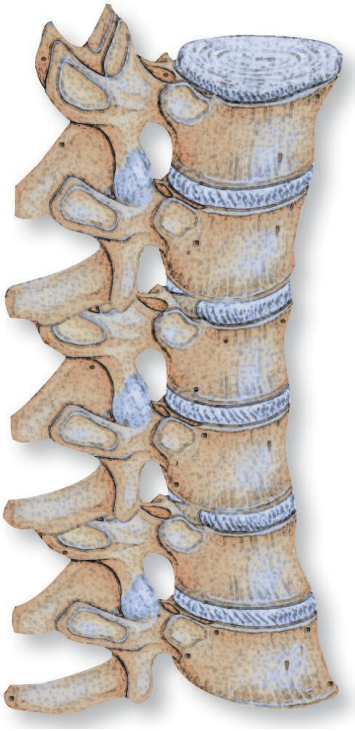
NEW YORK STATE OF OPPORTUNITY. Department of Health



SPINAL CORD INJURY RESEARCH BOARD

NYS SCIRB Report

January 1, 2022, to December 31, 2023

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 302,000 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 $429,348 to more than $1,315,554, with annual costs thereafter ranging from approximately $52,150 to $228,450.[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, 2023. Web. 15 November 2023. https://www.nscisc.uab.edu/

The SCIRB's mission and goal is to:

1. Seek major advances toward a cure ant 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 2023, the current composition of the SCIRB included three (3) researchers, five (5) clinicians, and two (2) spinal cord-injured persons. Members serve four-year terms. Five (5) new appointments were made in 2023 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 both fiscal year 2022-23 and fiscal year 2023-24, $8.5 million was programmed to support SCI research.

The SCIRB held one (1) meeting in 2022 (see Section IV below). By the end of 2022 three (3) procurements had been released by the New York State Department of Health, Wadsworth Center, Extramural Grants Administration on behalf of the SCIRB.

The SCIRB held two (2) meetings in 2023 (see Section IV below). By the end of 2023, 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 web site at: https://www.wadsworth.org/extramural/spinalcord/meetings.

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

No changes were made to the SCIRB's bylaws in 2022 or 2023. 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 May 11, 2022, meeting, the SCIRB recommended funding for two (2) awards from the "Translational Research Projects in Spinal Cord Injury (Round 4)" Request for Applications (RFA) for a total of $7.57 million. These five (5) year awards began in October 2022.

The SCIRB also recommended funding for nine (9) awards from the "Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activities (IDEA) in Spinal Cord Injury (Round 5)" RFA for a total of $5.7 These two (2) and three (3) year awards, respectively, began in October 2022.

At its May 25, 2023, meeting the SCIRB recommended funding or seven (7) awards from the "Predoctoral and Postdoctoral Fellowships in Spinal Cord Injury Research (Round 5)" Request for Applications (RFA) for a total of $1.22 million. These two (2) year awards began in October 2023.

The SCIRB also recommended funding for eight (8) awards from the "Projects to Accelerate Research Translation (PART) and Innovative, Developmental or Exploratory Activities (IDEA) in Spinal Cord Injury (Round 6)" RFA for a total of $5.3 million. These two (2) and three (3) year awards, respectively, began in October 2023.

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

Previously Recommended SCI Research Contracts

By March 2022, the Institutional Support for SCI Research in New York State (Round 6) contracts completed their final year. This opportunity made SCI research funds available to organizations located within New York State that demonstrated a current notice of funding award or renewal from a peer-reviewed SCI research project conducted by a principal investigator employed at their organization. Twenty (20) five (5) year awards were approved to provide additional support for SCI research projects through the purchase of laboratory supplies, salaries, equipment, and other customary expenses necessary to support research efforts. The scientific progress resulting from these SCI funded projects can be found in Appendix 2.

In May 2022, three (3) PART awards from the PART and IDEA in SCI (Round 3) contracts began their final year since they received no-cost extensions (NCEs). The four (4) IDEA

contracts completed their final year. The scientific progress resulting from these three (3) and two (2) year awards, respectively, can be found in Appendix 2.

By August 2022, five (5) Individual Predoctoral and Post Doctoral Fellowships (Round 4) contracts completed their final year. The scientific progress resulting from these three (3) year contracts can be found in Appendix 2.

By October 2023, five (5) IDEA awards from the PART and IDEA in SCI (Round 5) contracts began their final year. The scientific progress resulting from these three (3) year awards can be found in Appendix 2.

By November 2023, one (1) PART award from the PART and IDEA in SCI (Round 4) contracts begins its final year. Seven (7) IDEA awards from the PART and IDEA in SCI (Round 4) completed their final year. One (1) of the eight (8) IDEA awardees from the Research Foundation of SUNY Albany, Dr. Ben Szaro, declined his award and announced his retirement. The scientific progress resulting from these three (3) and two (2) year awards, respectively, can be found in Appendix 2.

In July 2023, thirteen (13) Institutional Support (Round 7) contracts began their first year. The Scientific progress resulting from these five (5) year awards can be found in Appendix 2.

In October 2023, eight (8) Individual Predoctoral and Postdoctoral Fellowships in SCI (Round 5) contracts began their first year. The summary of these three (3) year awards can be found in Appendix 2.

By April 2023, two (2) Transitional Research Projects in SCI (Round 2) awards completed their final year. These contracts ended in April 2022, but were granted NCEs to continue until April 2023. The Scientific progress resulting from these four (4) year awards can be found in Appendix 2.

In October 2023, four (4) IDEA and four (4) PART awards from the PART and IDEA in SCI (Round 6) contracts began their first year. The summary of these two (2) and three (3) year awards, respectively, can be found in Appendix 2.

NYS SCI Research Symposium

The SCIRB discussed scheduling a future NYS SCI Research Symposium at their business meetings in 2022 and 2023. 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.

At their 2023 meetings SCIRB members discussed forming a subcommittee to investigate the feasibility of holding a Symposium, with four SCIRB members showing interest, along with a representative from NYS Department of Health, Wadsworth Center, Extramural Grants Administration to act as a liaison for the Department of Health.

Appendix 1

Translational Research Projects in SCI (Round 4)

$7.57 million in the form of two (2) Translational Research Projects in SCI awards were recommended on May 11, 2022, to the NYS Commissioner of Health.

Projects are five (5) year awards.

Organization	Research Category	Project Title	PI	Recommended Funding
Columbia University	Rehabilitation	Improving Balance After SCI Using a Robotic Upright Stand Trainer	Sunil K. Agrawal, Ph.D.	$3,995,925
The Feinstein Institute for Medical Research	Rehabilitation	Constant and Cortically Modulated Transcutaneous Spinal Cord Stimulation for the Treatment of Upper Extremity Impairment	Chad E. Bouton, M.S.	$3,570,469
			Total 2 Awards	$7,566,394

Predoctoral and Postdoctoral Fellowships in Spinal Cord Injury Research (Round 5)

$1.22 million in the form of eight (8) Predoctoral and Postdoctoral Fellowship awards were recommended on May 25, 2023, to the NYS Commissioner of Health.

Projects are two (2) year awards.

Organization	Research Category	Project Title	PI	Recommended Funding
Winifred Masterson Burke Medical Research Institute	Postdoctoral	Restoration of Motor Function Following SCI via Optical Stimulation	Yutaka Yoshida, Ph.D.; Alzahraa Amer, Ph.D., P.T.	$180,581
Columbia University	Postdoctoral	Improving Trunk Control While Seated on Wheelchairs in Individuals with SCI Using Robotics	Sunil K. Agrawal, Ph.D.	$190,000
The Research Foundation of CUNY obo City College of New York	Predoctoral	Activity and Connectivity Maintain Premotor Interneuron Viability After SCI	John H. Martin, Ph.D.	$118,000
Rensselaer Polytechnic Institute	Predoctoral	Novel Poly (Pro-Gabapentin) Films to Provide Neuroprotection and Increase Neurite Extension	Ryan J. Gilbert, Ph.D.; Edmund F. Palermo, Ph.D.	$122,400
Columbia University	Predoctoral	Improving Trunk and Neck Coordination During Reaching Tasks with a Robotic Neck Brace in Individuals with SCI	Sunil K. Agrawal, Ph.D.	$116,000
Icahn School of Medicine at Mount Sinai	Postdoctoral	Multi-Drug Combination Effects on Physical Therapy-Enabled Recovery After SCI	Ravi Iyengar, Ph.D.	$191,978
Columbia University	Postdoctoral	Functional Dissection of the Rat Corticoreticular Pathway in SCI	Jason B. Carmel, M.D., Ph.D.	$180,000
Cornell University	Predoctoral	Examine the Effects Goldfish Extracellular Matrix (ECM) Hydrogel and Chondroitinase ABC (ChABC) in Injured Mice	Yadong Wang, Ph.D.	$122,400
			Total 8 Awards	$1,221,359

PART and IDEA (Round 5)

$5.75 million in the form of four (4) PART and five (5) IDEA awards were recommended on May 11, 2022, to the NYS Commission of Health.

Projects are three (3) years for PART and two (2) years for IDEA awards.

Organization	Funding Mechanism/ Research Category	Project Title	PI	Recommended Funding
Albany Research Institute, National Center for Adaptive Neurotechnologies	IDEA/Rehabilitation	Operant Conditioning of Somatosensory Evoked Potentials to Improve Motor Function After SCI	Disha Gupta, Ph.D.	$356,538
Icahn School of Medicine at Mount Sinai	PART/Rehabilitation	Augmentation of Bladder Function by Transcutaneous Spinal Cord Stimulation After Conus Medullaris Injury in Primates	Leif A. Havton, M.D., Ph.D.	$995,000
Sloan Kettering Institute for Cancer Research	IDEA/Cellular Regeneration & Therapeutics	Promoting Neuronal Regeneration by Targeting the Alpha Secretase Cleavage of p75 With Monoclonal Antibodies	Dimitar B. Nikolov, Ph.D.	$360,000
Stony Brook University	PART/Cellular Regeneration & Therapeutics	Therapeutic Intermittent Hypoxia to Reduce Detrusor Overactivity and Symptom Severity in Chronic Incomplete SCI: Translation and Mechanisms	Irene C. Solomon, Ph.D.	$986,610
The City College of New York	IDEA/Cellular Regeneration & Therapeutics	Nucleolipid Signaling for Spinal Cord Regeneration	Ashiwel S. Undieh, Ph.D.	$360,000
The City College of New York	PART/Rehabilitation	Leveraging LTP to Promote CST Axon Sprouting in the Spinal Cord	John Martin, Ph.D.	$982,800
Winifred Masterson Burke Medical Research Institute DBA Burke Neurological Institute	IDEA/Cellular Regeneration & Therapeutics	Role of SPARC in Pathological Wound Healing After SCI	Edmund R. Hollis, Ph.D.	$360,000
Winifred Masterson Burke Medical Research Institute DBA Burke Neurological Institute	PART/Rehabilitation	Enhancing Nerve Transfer Surgery to Restore Hand and Arm Function in Chronic Tetraplegia	Edmund R. Hollis, Ph.D.	$990,000
Winifred Masterson Burke Medical Research Institute DBA Brain and Mind Research Institute	IDEA/Cellular Regeneration & Therapeutics	Mechanisms Controlling early and segmentally distinct loss of long-distance corticospinal axon regenerative ability	Vibhu V. Sahni, Ph.D.	$360,000
			Total 9 Awards	$5,750,948

PART and IDEA (Round 6)

$5.3 million in the form of four (4) PART and four (4) IDEA awards were recommended on May 25, 2023, to the NYS Commissioner of Health.

Projects are three (3) years for PART and two (2) years for IDEA awards.

Organization	Funding Mechanism/ Research Category	Project Title	PI	Recommended Funding
Icahn School of Medicine at Mount Sinai	PART/Rehabilitation	Biomarkers of SCI Pain Evolution During Acute Rehabilitation (BioSPEAR)	Thomas Bryce, M.D.	$910,611
Winifred Masterson Burke Medical Research Institute	PART/Cellular Regeneration & Therapeutics	Ephrin-Mediated Cortical Motor Circuit Rewiring	Edmund Hollis, Ph.D.	$988,622
Icahn School of Medicine at Mount Sinai	IDEA/Cellular Regeneration & Therapeutics	Investigate Glial Communication in Neural Repair After SCI	Hongyan (Jenny) Zou, M.D., Ph.D.	$360,000
Winifred Masterson Burke Medical Research Institute	IDEA/Cellular Regeneration & Therapeutics	Structural Plasticity of Cortico-Brainstem Projections After SCI and Their Contribution to Functional Recovery	Vibhu Sahni, Ph.D.	$360,000
Bronx Veterans Medical Research Foundation	PART/Rehabilitation	Optimizing Spinal Cord Associative Plasticity to Enhance Response to Hand Training in Cervical SCI	Noam Harel, M.D., Ph.D.	$946,581
University of Rochester	IDEA/Cellular Regeneration & Therapeutics	PDE10A Treatment for Neuropathic Pain After SCI	Bradford C. Berk, M.D., Ph.D.	$359,294
Winifred Masterson Burke Medical Research Institute	IDEA/Cellular Regeneration & Therapeutics	The Contribution of Wallerian Degeneration to Neural Tissue Inflammation and Axon Regeneration	Edmund Hollis, Ph.D.	$360,000
Bronx Veterans Medical Research Foundation	PART/Cellular Regeneration & Therapeutics	Novel Targeting Nanotherapeutics for Functional Recovery After Acute SCI	Welping Qin, M.D., Ph.D.	$990,000
			Total 8 Awards	$5,275,108

Institutional Support (Round 7)

$3.9 million in the form of thirteen (13) Institutional Support awards were recommended on May 25, 2023, to the NYS Commissioner of Health.

Projects are five (5) year awards.

Organization	Project Title	PI	Recommended Funding
Winifred Masterson Burke Medical Research Institute	Enhancing Nerve Transfer Treatment for Chronic SCI	Edmund R. Hollis, Ph.D.	$300,000
The Research Foundation for SUNY – Stony Brook	Neuroprotective Strategies to Minimize SCI Tissue Damage and Improve Bladder and Respiratory Function	Irene C. Solomon, Ph.D.	$300,000
The Research Foundation for SUNY – Downstate Health Sciences University	Dissemination of a Tool for Data-Driven Multiscale Modeling of Brain Circuits	Salvador Dura-Bernal	$300,000
Bronx Veterans Medical Research Foundation	Synergy Between Exercise and a Connexin Hemichannel Blocker After SCI	Christopher Cardozo	$300,000
Icahn School of Medicine at Mount Sinai	The Role of AHR in Regulating Axon Regeneration	Hongyan Zou, M.D., Ph.D.	$300,000
Regenerative Research Foundation	Assessment of Selective Inhibitors of Nuclear Export (SINE) Following SCI	Caitlin Hill	$300,000
University of Rochester	Promoting Recovery by Inhibiting PDE10A-Mediated Inflammation	Bradford Berk	$300,000
The Research Foundation of CUNY – Staten Island	Priming with High-Frequency Trans-Spinal Stimulation to Augment Locomotor Training Benefits in SCI	Noam Y. Harel, M.D.	$300,000
The Feinstein Institute of Medical Research	Biomarkers of Immune Dysfunction and Vaccine Responsiveness in People with Chronic Traumatic SCI	Dr. Ona Bloom	$300,000
Rensselaer Polytechnic Institute	Polymerized Estrogen Microfibers in Injectable Hydrogels for Astrocyte-Mediated Neurite Guidance and Protection	Edmund F. Palermo, Ph.D.; Ryan J. Gilbert, Ph.D.	$300,000
The Trustees of Columbia University in the City of New York	Wheelchair Robot for Active Postural Support (WRAPS) of People with SCI	Sunil K. Agrawal, Ph.D.	$300,000
The Research Foundation of CUNY obo City College of New York	Strengthening SCI Research at the CUNY School of Medicine	John H. Martin, Ph.D.	$300,000
Albany Research Institute, Inc.	Operant Conditioning of Somatosensory Evoked Potentials to Improve Motor Function After SCI	Jonathan R. Wolpaw, M.D., Ph.D.	$300,000
		Total 13 Awards	$3,900,000

Appendix 2

Scientific Progress Resulting from SCI Research Board Funded Projects

PART and IDEA in SCI (Round 6)
IDEA Contract Terms 10/01/2023-09/30/2025; PART Contract Term 10/01/2023-09/30/2026

8 Awards, New 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 one of the most common and problematic secondary conditions following spinal cord injury (SCI). More than 80% of persons with SCI report pain throughout their lifetimes, which demonstrates that available treatments are not effective for everyone and suggests that the underlying mechanism of pain after SCI is still unknown. There remain substantial gaps in knowledge of the temporal evolution of neuropathic pain (NeuP), predictive factors for its development, and molecular mechanisms underlying NeuP that may serve as therapeutic targets. These gaps are most evident during the acute period after SCI, a period that is important as this is the time when neuroplasticity is prominent and neurological changes most commonly occur and there exists the greatest potential for interventional impact for this pervasive problem. The goal of this project is to improve the early diagnosis and effective treatment of NeuP after SCI. Our first objective is to document the experience of NeuP after SCI during the period of robust neuroplasticity during acute inpatient rehabilitation (AIR) when NeuP often develops or changes. We will also study the impact of administered standard-of-care treatments, both pharmacological and non-pharmacological, on the experience and trajectory of NeuP during this acute period. Our second objective is to identify a novel molecular biomarker signature of NeuP during AIR using hypothesis-driven and unbiased approaches, while our third objective is to explore the prognostic relationships of molecular biomarkers, clinical characteristics, and psychosocial factors associated with NeuP present at AIR discharge to the presence of persistent NeuP at 6 months post-injury. To accomplish these three objectives, we will employ a longitudinal repeated measures cohort design in a study of persons with traumatic SCI with assessments performed throughout AIR with an additional assessment at 6 months post-injury to address three specific aims. First, we will delineate the trajectory of the experience of NeuP during AIR using standard measures including evaluating the effects of treatments on this trajectory. Second, we will determine if elevated levels of inflammatory mediators are biomarkers of NeuP at admission and discharge from AIR. Specifically, we will measure levels of the pro-inflammatory alarmin HMGB1 (mRNA levels) and its associated signaling molecules in the circulation as we hypothesize that HMGB1 and molecules associated with its signal transduction cascade will be elevated in participants with NeuP as compared to participants without NeuP. We will also perform RNA-Seq of whole blood to determine genes that are differentially expressed in participants with and without

NeuP. Within each participant, we will also determine genes differentially expressed from admission to discharge that correlate with the presence of NeuP and NeuP intensity. Third we will explore the potential of the inflammatory mediators just mentioned, as well as clinical characteristics known to be associated with NeuP to predict the long-term persistence of NeuP at 6 months post-injury. These aims address a major gaps in knowledge including (1) delineation of the effects of therapeutic interventions during a time in which the injured nervous system is at its most plastic, (2) the identification of molecular biomarkers for NeuP which will shed light on the underlying mechanisms of NeuP and provide for potential preemptive or active treatment targets, and (3) an exploration of the relationship between psychosocial factors, clinical characteristics, and molecular signatures contributing to the persistence of NeuP after SCI.

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

Introduction/Background: Restoring voluntary motor control after spinal cord injury (SCI) will rely on the plasticity of the corticospinal tract, the primary pathway for movement in humans and non-human primates. Sprouting of intact corticospinal axons after unilateral central nervous system (CNS) injury occurs in animal models and is thought to underlie the spontaneous recovery of motor control observed in individuals with Brown-Sequard unilateral paralysis. While novel midline-crossing sprouts from intact corticospinal neurons have been demonstrated to form synaptic contacts and express markers of connectivity in the spinal cord, the potential for such newly formed circuits to support behavioral recovery or integrate into cortical motor networks is unknown. The long-term goal is to establish therapeutic interventions to enhance circuit recovery and alleviate function lost to SCI. The overall objective of this proposal is to determine the effects of enhanced cortical motor circuit rewiring on the re-establishment of a functional motor circuit after injury. The central hypothesis is that conditional deletion of EphA4 from the contralesional motor cortex will increase functional connectivity of uninjured corticofugal motor axons throughout the motor circuit. The rationale for the proposed research is that determining how corticofugal circuit plasticity shapes recovery will support the development of novel therapeutic interventions for traumatic central nervous system injury including stroke and SCI. The following three specific aims are proposed: 1) Determine the structural plasticity of rewired corticofugal circuits induced by EphA4 deletion; 2) Record the activity changes in corticospinal neurons induced by EphA4 deletion; and 3) Identify the functional contribution of rewired corticospinal circuits induced by EphA4 deletion. For the first aim, the approach will be to use a fluorescent reporter to assess axonal growth in the spinal cord and brainstem in combination with rehabilitation on a skilled forelimb task to test effects on motor recovery. In the second aim, the approach will be to retrogradely transduce contralesional corticospinal neurons to express the genetically engineered calcium indicator GCaMP7f prior to injury and to record changes in calcium transients across rehabilitation. In the third aim, the approach will be to selectively target supraspinal motor circuits through dual-viral transduction to express the diphtheria toxin receptor to individually test their role in rehabilitation-mediated recovery. The proposed studies are innovative in that they shift the focus of motor circuit rewiring onto the ability of cortical motor networks to incorporate changes in motor circuitry. The

proposed studies are significant because they will provide a detailed understanding of how rehabilitation shapes circuit rewiring, and influences injured and newly formed cortical motor circuits. The expectation is that completion of the proposed research will determine the extent of circuit rewiring and the contribution of motor circuit plasticity to movement recovery after central nervous system injury. These findings will establish a foundation to guide the development of therapeutic strategies targeting movement recovery.

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: Communications between glial cells play a critical role for wound repair after spinal cord injury (SCI). In response to injury, astrocytes and microglia are mobilized to form a protective glial barrier that separates the injury core from healthy spinal cord tissues. The glial barrier also facilitates debris clearing, limits inflammatory spread, and promotes wound compaction, thereby minimizing lesion size, maximizing repair area, and providing permissive substrates for axon regeneration. Building such a protective glial barrier requires coordinated physical interaction and spatial organization of glial cells in a process termed wound corralling, wherein reactive astrocytes in the injury penumbra encircle and confine phagocytic immune cells in the lesion core. However, the signaling mechanisms remain incompletely understood.

   Recent studies from my laboratory have uncovered an important role of axon guidance receptor Plexin-Bs for neural repair after SCI. We showed recently that Plexin-B2 upregulation in microglia and macrophage is critical for wound corralling. Our new data revealed that Plexin-B1 also plays a pivotal role for wound healing. Interestingly, we found that Plexin-B1 is predominantly induced in reactive astrocytes; Plexin-B1 deletion resulted in glial disorganization and worsened moto sensory recovery after SCI. These exciting data prompted us to formulate our central hypothesis that Plexin-B1 mediates astrocyte activation and glial organization in forming the protective glial barrier and astroglial bridge across lesion site after SCI. In Aim 1, we will conduct functional studies using glial co-culture systems to test the hypothesis that Plexin-B1 functions to resolve cell collision and provide guidance for cellular alignment. In Aim 2, we will extend our in vivo SCI studies using conditional deletion of Plexin-B1 in astrocytes to pinpoint cell type-specific roles of Plexin-B1 in organizing astroglial alignment and wound corralling after SCI. We will also conduct spatially resolved transcriptomics combined with single cell analysis to characterize niche-specific glial cell signaling network and the role of Plexin-B1. Data from this project, together with our recent published work on Plexin-B2, will provide a more comprehensive picture of the corralling process that is safeguarded by cell-type specific roles of Plexin-B1 (in reactive astrocytes) and Plexin-B2 (in microglia) for glial cell organization and wound healing. Understanding the molecular mechanisms governing astrogliosis in forming protective glial barrier and astroglial bridge will point to new ways to improve functional outcome 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: The cortex regulates movement through both, direct connections with the spinal cord via corticospinal neurons (CSN), and indirect connections through cortico-brainstem neurons (CBN). To date, there has been no approach that can distinguish between these two subpopulations that reside interdigitated in cortex. CSN axons are damaged by spinal cord injury (SCI), and they respond to the injury by sprouting new collaterals in the spinal cord above the level of the lesion, including into the brainstem. However, whether CBN axons also show plasticity after SCI remains completely unknown. Evidence in the field suggests that CBN plasticity can contribute to recovery after nervous system injury. We have developed novel tools that can address this fundamental question for the field. We have recently established novel Cre mouse lines that enable, for the first time in the field, molecular access to these distinct subpopulations i.e., they allow us to distinguish between CBN and CSN. We have also established a new machine learning platform for automated registration of distinct brainstem nuclei. Using this method, we can now quantify axonal projections and synaptic connections between the cortex and distinct nuclei enabling rigorous quantitative assessment of plasticity of connections in response to SCI. Together, using these tools, we can now specifically investigate CBN axonal plasticity in the brainstem in response to SCI as distinct from CSN plasticity. Further, we will also investigate the potential role of CBN in spontaneous functional recovery after SCI. This work will therefore establish CBN as potential targets for therapeutic approaches aimed at enhancing recovery after SCI. Our long-term goal is to enhance recovery after SCI. Towards this goal, our overall objective is to investigate whether CBN exhibit plastic changes in response to SCI and whether this is distinct from the plastic changes that occur within CSN. We will also test the role of these neurons, as distinct from CSN, in spontaneous recovery after 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: Most individuals with Spinal Cord Injury (SCI) retain spared neural circuitry at and below the lesion. Task-oriented physical exercise is the bedrock of neurorehabilitation. However, exercise alone does not usually suffice to mediate significant long-term recovery from SCI. Hence, the glaring need for combinatorial interventions that can activate spared circuits to mediate functional recovery.

Our group has promising preliminary findings from experiments with spinal cord associative plasticity (SCAP). In SCAP, synchronized pulses of cervical spinal cord stimulation can facilitate hand muscle responses to cortical stimulation, suggesting the potential to facilitate cortically mediated volitional movement. However, we do not know the best ways to apply SCAP repetitively, especially in conjunction with exercise, to achieve lasting improvements in synaptic strength and clinical function. What pulse frequency and pattern? Should multiple bouts be delivered per session? Should multiple bouts of different interventions be given consecutively or

interleaved? Do the ideal intervention parameters vary across individuals? Do inflammatory mediators or neurotrophic factors influence responsiveness? This proposed trial will use a multiple-crossover “n-of-1” design to thoroughly answer these questions.

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

   Introduction/Background: Neuropathic pain is one of the major causes of morbidity in spinal cord injury (SCI) persons. Currently, mechanisms underlying this complication are poorly understood. Cytokines and activated immune cells that prolong inflammation within SCI lesions exacerbate tissue damage and cause systemic inflammation. It has been suggested that NLRP3 inflammasome activation, which produces IL-1β, is the major cause of neuropathic pain. Unfortunately, to date, there are no clinically approved drugs that selectively target the NLRP3 inflammasome for treating neuropathic pain. My lab has studied fundamental mechanisms of vascular remodeling and inflammation. A genome-wide association study in 17 inbred mouse strains identified Phosphodiesterase 10A (PDE10A), an enzyme that degrades cyclic AMP and cyclic GMP, as a candidate gene for the vascular response to injury and inflammation. Preliminary data regarding the role of PDE10A in inflammation include: 1) In our recent study of PDEs in cardiac hypertrophy and acute lung injury, PDE10Aknockout or inhibition by TP-10 protected mice from heart failure and lung inflammation. 2) PDE10A inhibition by MP-10 significantly improved motor function following sciatic nerve injury. 3) To define the role of PDE10A in SCI, we performed T9 contusion injury and found that PDE10A and the key inflammasome gene, NLRP3, were increased on days 7 and 42 after SCI. In mice treated with MP-10, NLRP3 expression was significantly decreased, as well as muscle atrophy, suggesting increased neuron recovery. 4) Stimulation of inflammasome-mediated inflammatory cytokines such as IL-1β requires both priming (e.g., increased expression of NLRP3) and subsequent assembly and activation (e.g., K+ efflux). Inhibiting PDE10A with TP-10 or MP-10 dramatically decreased secretion of IL-1β in cultured macrophages. Based on our data and the literature, we hypothesize that PDE10A inhibition will reduce neuropathic pain by limiting acute inflammation (IL-1β secretion) and chronic inflammation (M1 macrophage accumulation) after SCI. To prove this hypothesis, we propose two aims. Aim 1: Characterize the role of PDE10A in inflammation and neuropathic pain after SCI in mice. Aim 2: Determine the effect of MP-10 on chronic neuropathic pain after SCI. The results of this research should define the role of PDE10A in inflammation caused by SCI and show that PDE10A inhibition will reduce neuropathic pain; thereby improving the quality of life for SCI persons.

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: Traumatic spinal cord injury (SCI) causes neural tissue destruction at the lesion epicenter, Wallerian degeneration (WD) of distal axon

fragments, and tissue damage triggers a strong immune response. In the peripheral nervous system (PNS), local inflammation-resolving macrophages drive axon regeneration and are molecularly distinct from the WD-associated macrophages distal to the injury site. Mice deficient for the NAD degrading enzyme Sarm1 show impaired WD, resulting in reduced PNS regeneration and impaired monocyte maturation in the distal nerve. While axon protection following spinal cord injury is thought to be beneficial, the impact of protecting axons from WD on experimentally induced axon regeneration has not yet been explored. The overall objective of this proposal is to determine the significance of WD to axon regeneration in the injured spinal cord and to describe the immune response to WD in the injured mammalian CNS. The central hypothesis is that WD triggers neural tissue inflammation and is necessary for CNS axon regeneration following spinal cord injury. The rationale behind the proposed research is that determining how the immune response is shaped by WD will disambiguate the secondary immune response to injury from the inflammatory remodeling of distal white matter and help determine how axon protective strategies can shape regenerative therapies. The following two specific aims are proposed: 1) Determine the role of Sarm1 in the immune response after SCI; and 2) Assess the contribution of delayed WD in Sarm1 deficient mice to dorsal column axon regeneration after SCI. For the first aim, the approach will include flow cytometry, single nuclei transcriptomics, and immunofluorescence labeling of spinal cord tissue after thoracic contusion SCI. In the second aim, the approach will be to apply a sciatic nerve crush for conditioning lesion of sensory neurons in wild-type and Sarm1-/- mice, followed by a thoracic contusion SCI. The proposed studies are innovative in that they will address whether axon protective therapies may negatively impact therapies aimed at promoting axon regeneration following SCI. The proposed work is significant because it will generate new knowledge about the immune response triggered by WD in the injured CNS. The expectation is that completion of the proposed work will have defined the immune response in the injured spinal cord in mice with impaired WD and a determination of how WD reshapes the injured spinal cord and the role it plays in CNS axon regeneration. These findings will provide a foundation to guide the development of therapeutic strategies targeting axon protection after traumatic SCI.

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: Spinal cord injury (SCI) is a catastrophic medical problem that causes loss of sensory, motor, and autonomic function. Methylprednisolone (MP) is only FDA approved agent that is being used by some clinicians to improve function after acute injury. However, the use of this drug remains controversial because the modest protective functions on nerve cells are frequently overshadowed by the unfavorable side effects to the rest of the body, including infection, myopathy, neuropathy, gastrointestinal hemorrhage, disorders of carbohydrate metabolism, and, possibly, even more rapid bone deterioration. As such, identification, and development of a safe, effective, and affordable therapy to prevent the secondary neurological deficits after acute SCI remains a high priority. To address this major medical challenge, we have developed a nanoparticles-conjugated MP (Nano-MP; Patent PCT-US20-054559), which is composed of MP and a carrier (N2-hydroxypropyl methacrylamide). Our exciting preliminary data demonstrated that the

Nano-MP, by a single administration, can be preferentially delivered to the site of the injured spinal cord in a rodent model of SCI, where the drug is sequestered and retained mainly by infiltrating inflammatory cells (inferred from the action of the parent MP molecule) for several days. Compared to conventional intravenous delivery of the MP molecule, the Nano-MP administration significantly improve neuroprotection (e.g., reduced lipid peroxidation, inflammation, neural damage) and functional outcomes. The Nano-MP appears not to accumulate in other tissues or remote organs to cause side effects, thus mitigating musculoskeletal defects (a few appreciated biomarkers of the adverse systemic effects of MP) at 2 days post-SCI.

The main goal of the proposed study is to further develop nanotechnology-enabled MP for targeted delivery as a novel agent to improve functional outcomes more significantly with minimal side effects after SCI. We hypothesize that the targeted MP delivery to the injury site will have superior therapeutic efficacy to improve functional recovery after SCI (e.g., because of greater delivery efficiency, this approach will lead to reduced lipid peroxidation, inflammation, neural damage, and lesion) while markedly reducing adverse systemic side effects compared to conventional intravenous delivery of the parent MP molecule. To test this hypothesis and to achieve our research goal, a series of preclinical experiments are proposed as follows:

Aim 1: To screen and identify optimized Nano-MP with maximal drug potency to support the proposed activities and to validate if the modified Nano-MP can more efficiently reduce lipid peroxidation and promote neuroprotection in contusion SCI rats.

Aim 2: To determine whether Nano-MP improves functional recovery after a contusion SCI in rats. Aim 3. To study if the improved functional recovery by Nano-MP is associated with markedly reduced adverse side effects after acute SCI.

PART and IDEA in SCI (Round 5)
IDEA Contract Terms 10/01/2022-09/30/2024; PART Contract Term 10/01/2022-09/30/2025

Progress Reporting Period
10/01/2022-03/31/2023

9 Awards, New Procurement Total: $5,750,948

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, myelin inhibitors, such as the myelin-associated glycoprotein (MAG), Nogo-A and oligodendrocyte myelin glycoprotein (OMgp), bind to and signal through a single receptor/co-receptor complex comprising of NgR1, Lingo-1 and p75. Consequently, p75 is cleaved by the alpha-secretase ADAM17, followed by gamma-secretase, triggering intracellular signaling that prevents the re-growth of axons. The interaction of p75 with ADAM17, which is central to the events surrounding spinal cord injury, has not yet been studied. Previously, we showed that the ganglioside GT1b facilitates the assembly of the NgR1/Lingo-1/p75/Nogo-A signaling complex (5-component/5-mer complex). To study these interactions, we have raised anti-ADAM17 specific monoclonal antibodies (mAbs) that disrupt the binding of ADAM17 to substrates implicated in cancer biology/axon guidance and inhibit the signaling pathways mediated by ADAM17. We will investigate the potential of these mAbs to inhibit p75 cleavage and abrogate the downstream signaling pathway that prevents neuronal regeneration.

   Progress Towards Specific Aims: (i) Biochemical pull-down experiments/ELISA-based assays demonstrate that ADAM17 interacts with the neuronal receptor/co-receptor complex, in the presence and absence of the MAG ligand, but not with isolated (unbound) p75; (ii) ELISA-based studies show that the two anti-ADAM17 scFv's partially inhibit the binding of ADAM17 ectodomain to the 5-component complex; (iii) we have initiated cryo-EM studies with ADAM17 bound to the mAbs and scFv's; (iv) Using the NG108-15 cell line, we are evaluating the ability of the anti-ADAM17 mAbs to prevent p75 cleavage.

   Future Directions: (a) Characterize the assembly of the functional 5-component signaling complex; (b) Evaluate the ability of the anti-ADAM17 mAbs to abrogate the interaction of ADAM17 with the 5-component complex; (c) Structural characterization of the ADAM17/mAb interactions.

   Impact: The three-dimensional structures of the 5-component signaling complex will reveal the essential molecular steps governing spinal cord injury and regeneration. Novel therapeutic mAbs characterized during this study will spur the development of new treatment strategies for spinal cord injury.

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. Nine participants have been enrolled, two of whom have completed six weeks of robotic training at one-year post-surgery. An additional three individuals have had nerve transfer surgery and will undergo robotic training in year two of the funding period.

Aim 2. Determine the regeneration-promoting effects of conditioning electrical stimulation in an animal model of radial nerve repair. The second aim of the study will test the pro-regenerative effects of electrical stimulation in a translational model of nerve cut and repair. IACUC approval for these studies has been secured and scheduling of surgeries is ongoing.

Future Directions: For aim 1, we will analyze data from the most recent participant to complete intensive, robotic rehabilitation during the next period. Additionally, we will continue to arrange surgical consultations for enrolled individuals and assess their eligibility for nerve transfer surgery.

For aim 2, baseline assessments and surgeries will be scheduled

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. The injured spinal cord, however, exhibits a robust capacity for neural plasticity, which promotes spontaneous functional recovery albeit 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 rats with SCI. While our observations are encouraging, the impact of therapeutic AIH as a strategy to improve bladder function in humans with SCI remains to be evaluated. Moreover, little is known about the neural mechanisms that underlie AIH-induced improvements in SCI. Therefore, this project is designed to initiate translation of our work (SA1: human subjects - *proof of concept pilot study*) and evaluate possible neural mechanisms that may underlie AIH-induced improvements in LUT function (SA2: preclinical rat studies).

Progress towards Specific Aims: We have conducted pilot experiments for SA2 to begin to evaluate the potential contribution of neuromodulatory serotonergic (5-HT) mechanisms in AIH treatment-induced improvements in LUT function. Preliminary data from these experiments show that administration of a broad spectrum 5-HT receptor antagonist prior to AIH exposure markedly attenuates AIH-induced changes/improvements in LUT function, suggesting that 5-HT-mediated mechanisms likely contribute to induction of the AIH-mediated effects.

Future Directions: We plan to continue with our preclinical studies investigating contributions of 5-HT mechanisms to AIH therapy-induced improvements in LUT function in rats with SCI, initiate similar experiments evaluating contributions of A_{2A} mechanisms, and initiate recruitment and preliminary studies in humans with SCI during the next reporting period.

Impact: This project will enhance our understanding of the therapeutic efficacy of AIH treatments on bladder function, symptom severity/bother, and urinary protein biomarkers in individuals with SCI and identify potential neuromodulatory mechanisms (which have yet to be determined in SCI) that contribute to AIH therapy-induced improvements in bladder function in SCI. As such, this work will also provide novel information about benefits of AIH therapies to improve clinical indices of bladder function in SCI and lay the groundwork to enable future clinical trials and enhance the potential for rapidly transitioning AIH therapies to clinical management of bladder dysfunction following SCI.

4. Winifred Masterson Burke Medical Research 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 NYS DOH, we developed a new model of experimental CST injury in mouse pups. Through this work, we 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. We 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. We 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. We 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: Since the beginning of this grant, we have worked toward generating results in Aim 2. In this Aim we hypothesized that environmental molecules limiting CST growth are topographically expressed in the dorsal spinal cord early in development. We aimed to transcriptionally profile the dorsal spinal cord with or without micro-SCI at 3 distinct spinal levels- cervical C2, thoracic T2, and thoracic T11, at 3 developmental times– P1, P4, and P7.

We have completed the sample acquisition for this analysis and confirmed that the RNA samples collected are adequate for RNA sequencing. cDNA libraries were prepared and the samples are being sequenced.

Future Directions: Once the sequencing results have been obtained, we will analyze them as proposed in Aim 2.

Using multiple comparisons, we will then answer the questions listed in the following table.

Question	**Groups being compared**	**Potential outcome**
How does the spinal environment change during normal development? Do these changes follow the same timeline in distinc segments?	Uninjured C2 from P1 vs P4 vs P7; uninjured T2 from P1 vs P4 vs P7; uninjured T11 from P1 vs P4 vs P7.	The spinal environment gets more inhibitory with time. These changes happen earlier in the cervical and later in the thoracic segments.
Is the spinal environment different in distinct segments before the injury?	Uninjured P1 C2 vs P1 T2 vs P1 T11; uninjured P4 C2 vs P4 T2 vs P4 T11.	At P1, the spinal environment is more inhibitory at C2 than at T2 and T11. At P4, the spinal environment is more inhibitory at C2, slightly less at T2, and not inhibitory at T11.

Does the injury trigger distinct changes in different spinal segments?	P1 C2 vs T2 lesion; P4 C2 vs T2 vs T11 lesion	Injury triggers different cellular responses depending on the injury level.

Impact: There is a critical need for this work since the nervous system has never been previously investigated in the context of loss of 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 conus medullaris (CM) and cauda equina (CE) portions of the spinal cord characteristically result in a clinical syndrome, which includes motor, sensory, and autonomic impairments affecting the lower body. Lower urinary tract (LUT) dysfunction is common with CM/CE forms of spinal cord injury (SCI) and typically presents with impaired micturition reflexes and detrusor underactivity (DU). Presently, there are no treatments available to reverse or mitigate the SCI-induced underactive bladder (UAB) associated with a conus medullaris syndrome (CMS). Our proposed studies aim to evaluate the potential utility of an emerging neuromodulation strategy in the form of non-invasive electrical stimulation of the spinal cord to augment LUT function after CM/CE injury in a large animal model. Our overall hypothesis is that reorganization of micturition reflexes and detrusor underactivity in response to a partial injury to the CM/CE portion of the spinal cord can be characterized and ameliorated by transcutaneous spinal cord stimulation (TSCS) in primates. Two specific aims will address our overall hypothesis:

SPECIFIC AIM1: To determine functional maps for TSCS-evoked detrusor contractions and activation of the external urethral sphincter (EUS), external anal sphincter (EAS), and pelvic floor muscles after a bilateral S1 ventral root avulsion (VRA) injury in male and female rhesus macaques. The TSCS-evoked activation of the detrusor, external sphincters, and pelvic floor muscle groups will be performed pre-operatively and at 1, 3, and 6 months after a bilateral S1 VRA injury. The studies will provide insights of pre- and post-operative variability in pelvic target-specific functional maps between subjects, sexual dimorphism, and bilateral S1 ventral root (VR) injury-induced plasticity of spinal cord circuits. The optimal site for TSCS-

evoked detrusor activation will be determined pre- and post-operatively in each animal and guide subsequent neuromodulation of LUT function after injury as outlined in Specific Aim 2.

SPECIFIC AIM 2: To determine the utility of TSCS to augment micturition reflexes and voiding function after a bilateral S1 VRA injury in male and female rhesus macaques. TSCS will be performed in attempts to enhance micturition reflexes and increase voiding efficiency (VE) after a bilateral S1 VRA injury. Comprehensive urodynamic studies, including cystometrogram (CMG) and EUS EMG recordings, will be performed without and with the addition of TSCS for functional LUT assessments both pre-operatively and at 1, 3, and 6 months after a bilateral S1 VRA injury. Functional mapping in Specific Aim 1 will allow for the identification of the optimal inter-spinous process site location for TSCS for each experiment.

The interpretation of functional mapping and neuromodulation of the LUT after a bilateral S1 VRA injury will be aided by additional morphological studies of lumbosacral ventral roots, including light and electron microscopic mapping of preganglionic parasympathetic fibers. Biopsies obtained intra-operatively of the bilateral S1 VRs will be procured, plastic embedded, and studied by light microscopy (LM) and transmission electron microscopy (TEM) for determining the number, myelination, and proportions of small, myelinated axons in the 0-4 μm diameter size range, representing preganglionic parasympathetic fibers. At the end of the study period, the bilateral L6, L7, S2, and S3 VRs will be similarly collected, processed, and evaluated by both LM and TEM, thereby allowing for an estimate of the degree of injury-induced denervation of autonomic pelvic targets, including the LUT. If successful, our studies will provide novel mechanistic insights of LUT function and contribute with important feasibility and utility data for the translation of TSCS to reverse DU after incomplete CM/CE forms of SCI in clinical studies.

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: People with spinal cord injury have motor impairments of various degrees due to damage to their descending and ascending connections between the brain and the spinal cord. Most rehabilitation research typically focuses on repair and rehabilitation of their descending connections through which brain controls the muscles. However, along with the impaired movement, they also experience impairments in sensation. Less attention is given to restore these connections that bring sensory information from the muscles to the brain. Sensory input is an essential component of normal motor function and loss of sensation can limit motor rehabilitation. The goal of this study is to enhance functional recovery in incomplete SCI (iSCI) by strengthening weak CNS responses to sensation with Targeted Neuroplasticity using a novel non-invasive brain computer interface.

Progress Towards Specific Aims: This study has 2 Aims: i) To develop and validate upper-limb somatosensory operant conditioning in healthy people and apply it in people with iSCI. Control group will receive no conditioning. ii) To assess its impact on hand/arm function and physiology. The sensory brain computer interface software

has been developed and is being currently tested and optimized with the hardware, along with preliminary testing in healthy people. Various sensory and motor assessment protocols for testing physiology have been optimized, including vibrotactile somatosensory assessments, and integration of neurophysiological data recording with robot-based kinematics.

Future Directions: The next aim is to recruit healthy people for a 10-week conditioning study followed by the same in people with cervical iSCI, and to assess the functional and physiological impact of the conditioning.

Impact: The work so far has led to: a) development of a novel sensory BCI that integrates with an open source BCI (BCI2000) and conditioning platform (EPOCS); b) vibrotactile sensory assessment setup including open-source vibration hardware assessment software useful in sensory R&D; c) integration of robot-based assessment with EEG hardware/software to assess physiology along with kinematics.

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: Nerve growth factors such as brain-derived neurotrophic factor (BDNF) are known to promote nerve cell resilience to injury as well as cell 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 inositide phospholipids from inactive PIP2 to activated PIP3. The greater the proportion of TrkB receptors that are stimulated, the greater the PIP3 response. Also, the greater the availability of PIP2, the more robust will be the production of PIP3. To make PIP2, the cell must first make another phospholipidcalled CDP-diacylglycerol (CDP-DG). The goal of our studies is to discover and characterize the drug-like properties of compounds that can promote BDNF signaling and nerve regeneration by increasing the synthesis of CDP-DG thereby boosting the supply of PIP2 to the TrkB receptors.

Progress towards Specific Aims: We have made progress on our first of two aims. We have tested about 6 of our selected compounds for effects on CDP-DG and on regrowth of mechanically injured nerve cells in culture. Results obtained remain generally consistent with our hypothesis.

Future Directions: For the next 6 months, we plan to test additional compounds for effects on CDP-DG and nerve cell regrowth. Work on Aim 2 is schedule for Year 2 of the project.

We experienced some setbacks due to failure-to-thrive or contamination of our primary neuron cultures. We have been assigned a dedicated tissue culture space in lab 906 Marshak Building, and we are currently moving our tissue culture operations into this better space. With this, we expect to make accelerated progress in the upcoming reporting period.

Impact: Observations made from work so far completed remain consistent with our main hypothesis, and we expect to continue to make progress on the aims of the project in the forthcoming reporting period.

There have been no changes to the aims or methods of the project.

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 injury, where 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 and preliminary 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. Motor cortex LTP and induced CST axonal outgrowth share molecular mechanisms. In this project, we study the link between LTP and CST axon growth with the aim of enhancing motor cortex LTP to enhance the CST axon growth state. In Aim 1, we will enhance motor cortex plasticity to grow new CST connections in healthy rats, and in Aim 2, after cervical contusion injury. Aim 3 will investigate translation from electrical neuromodulation to promote CST connections to using transcranial magnetic stimulation (TMS).

The premise for Aim 1 and 2 experiments is that motor cortex LTP, induced by TBS, can be enhanced by increasing cortical neuron excitability using an excitatory chemo genetic method, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). We hypothesize that this LTP enhancement will boost molecular signaling for CST axon growth and synaptogenesis and, in consequence, enhance growth of CST connections. The reason for pursuing Aim 3 is that, to translate our invasive electrical neuromodulatory approaches to the human, we must be able to replicate upregulation of CST axon growth using a phasic patterned non-invasive approach, TMS. We need to be able to use TMS intensity settings that are comparable to what are used for electrical stimulation, in terms of amount of muscle activation and extent of the motor cortex activated. The first step to achieve this goal is to develop a finite element method (FEM) model of the magnetic fields and their corresponding electric fields, the latter of which drive changes in neural functions.

Progress Towards Specific Aims: During the reporting period #1 we have made progress in Aim 1, to characterize the molecular signaling underlying axon growth, and Aim 3, to create a model of TMS of the rodent motor cortex. For Aim 1, we have biochemical data that now identifies a ‘biomarker’ for neuromodulation that is effective in promoting CST axon sprouting. The presence or absence of this marker can now be used to address the question of how boosting of plasticity in motor cortex

can enhance CST axon sprouting. We also have significant insights into a biochemical marker that tracks functional plasticity (motor cortex muscle evoked potential potentiation). Further, the response of these markers is comparable in naïve animals and in animals with a cervical contusion injury, paving the way to Aim 2 experiments. For Aim 3, we now have a mathematical model for predicting TMS settings that can lead to neuronal activation produced by electrical stimulation.

Future Directions: For the next reporting period we plan to pursue the chemo genetic bidirectional LTP modulation experiments further, with a focus on boosting plasticity in motor cortex using excitatory DREADD, to achieve the hypothesized upregulation of mTOR and concurrent downregulation of PTEN. Additionally, we plan to run quantitative simulation experiments for the FEM modeling of TMS-induced electric fields in MCX. We anticipate the hired postdoc to receive their visa and begin work during the next reporting period. That will enable us to move forward on the CST axon outgrowth studies.

Impact: Successful development of a neuromodulation strategy to boost brain plasticity for spinal connectivity will open new directions for biological therapies for SCI. Whereas we plan to use the chemo genetic approach, this has a potential non-invasive counterpart that is already in common experimental clinical use, transcranial direct current stimulation (tDCS). Support for our hypothesis of a causal link between motor cortex LTP and outgrowth would provide a novel therapeutic framework for promoting spinal motor system connections after SCI.

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: Our first specific aim is to characterize the temporal and spatial expression profile of SPARC after SCI. The experiments to analyze the temporal and spatial expression pattern of SPARC are ongoing, including immunohistochemistry and western blot analysis of SPARC expression at different time points after injury. Our preliminary data show an early increase in SPARC expression after injury, with a transient increase of SPARC fragments at 3 days post-injury. Our second aim is to determine the effect of SPARC deletion on scar formation and functional impairment after SCI. We have obtained and expanded a SPARC-null mouse line and have completed injuries, motor behavior analysis, and histological assessment of a first cohort of female and male mice. Our analysis shows SPARC-null animals display larger lesion volumes and a different motor recovery trajectory than wild-type control littermates.

Future Directions: We expect to finish acquiring samples and behavioral outcomes in new experimental groups to analyze SPARC's role in late injury progression (30 days

post-injury). We will perform experiments to further understand the role of SPARC in the deposition and stabilization of fibrotic components of the wound. We will also analyze how SPARC expression affects the wound-healing behavior of astrocytes after SCI by using clearing and *in-vivo* imaging techniques.

Impact: The contribution of our proposed research is that we 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. Our 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.

PART and IDEA in SCI (Round 4)
IDEA Contract Terms 11/01/2021-10/31/2023; PART Contract Term 11/01/2021-10/31/2024

Progress Reporting Period
11/01/2021-04/30/2022

9 Awards (1 Declined), Procurement Total: $3,490,176

1. **Cornell University**
   Yadong Wang, Ph.D.
   IDEA: $360,000
   Investigating Regenerative Goldfish Extracellular Matrix in Mammalian SCI

   Introduction/Background: Currently there are no effective treatment options for patients with SCI. As a result, every year more than 99% newly diagnosed SCI patients remain paralyzed to some extent for the remainder of their lives. This frightening statistic is the consequence of the complexity of SCI. After a mechanical insult initiates injury, different cell types within the spinal cord undergo detrimental changes that create a regeneration-inhibitory environment. These changes begin with strong inflammation, followed by cell death and scar formation. Researchers have begun to employ sophisticated engineering approaches to adequately address this complex multicellular injury environment and promote recovery in patients with SCI. In that regard, this project draws inspiration from a non-mammalian species with the inherent ability to fully recover from SCI – goldfish.

   Unlike mammals, goldfish can restore normal function within 4-12 weeks of SCI, depending on the severity of injury. Studies have revealed several neuron intrinsic proteins that contribute to regeneration in goldfish; however, no study has thoroughly explored the extracellular molecules that facilitate regeneration. As such, this study will be the first to conduct a proteomic analysis of spinal cord extracellular matrix (ECM) to determine key molecular differences between regenerating and non-regenerating species before and after SCI. Once goldfish ECM composition is analyzed, the research team will create an injectable hydrogel made of regenerative goldfish ECM and implant this new material into the injured mouse spinal cord to translate the inherent regenerative potential in goldfish to a mammalian species.

   Progress Towards Specific Aims: In this reporting period, the research team has successfully developed techniques to reproducibly induce SCI in goldfish that results in full recovery within approximately five (5) weeks of injury. Using this model, they have harvested regenerating spinal cord tissue from injured goldfish and begun the process of characterizing the protein composition over the five (5) weeks of recovery. In parallel, they have begun to develop an injectable thermos-responsive hydrogel using goldfish ECM that will eventually be the platform for their therapy to treat mammalian SCI.

   Future Directions: In the coming months the research team plans to finalize the analysis of goldfish and mouse spinal ECM before and after injury so that they can understand which goldfish proteins may play an important role in regeneration after

SCI. Moving forward with that data, they will develop an injectable hydrogel using goldfish ECM that they expect can facilitate tissue regeneration in mice after SCI.

Impact: By studying regeneration in mice that receive a goldfish ECM hydrogel and comparing to controls, the research team will reveal important new extracellular protein targets for future SCI research as well as develop a new injectable therapeutic that can be used as a biomaterial platform for future SCI research and treatment.

2. Icahn School of Medicine at Mount Sinai
Mar Cortes, M.D.
IDEA: $357,170
Long Term Effects of rTMS in Chronic Neuropathic Pain in People with SCI

Introduction/Background: Around 80% of people with SCI develop chronic neuropathic pain (CNP). This is a debilitating condition with major negative impacts on people's quality of life. Many treatment options have been offered (invasive stimulation and drugs) but provide limited effects and many secondary effects. There is a critical need to develop a new generation of therapies. Transcranial magnetic stimulation (TMS) is a non-invasive and painless brain stimulation technique that allows us to explore and change brain excitability. TMS has shown promising effects in neuropathic pain; however, there is not enough evidence of what are the long-lasting effects of the different protocols.

The research team’s hypothesis is noninvasive brain stimulation will induce neuromodulation leading to long-term analgesic effects in people with CNP after SCI since CNP is associated with maladaptive plastic changes in the brain.

Thirty (30) SCI subjects with CNP in their hands will participate in this study, which will be a randomized sham-controlled trial with two (2) groups (real or sham high frequency repetitive TMS protocol at 20Hz). The protocol will be done daily for two (2) weeks. Clinical, functional, and neurophysiological evaluations will be assessed at baseline, post intervention and a follow up at six (6) weeks. The team’s objective is to evaluate the efficacy of real versus sham rTMS and investigate the short- and long-term effects on pain and the behavioral and neurophysiological qualities of responders and non-responders to this treatment.

Progress Towards Specific Aims: During this reporting period the team has submitted and received Institutional Review Board (IRB) approval and published the study protocol on a clinical trials national registry. They have also purchased and set up the equipment for the study and have built and customized a REDCap data collection platform. The team has been actively recruiting participants via inpatient and outpatient local departments, existing research databases, as well as hospital website and social media posts.

Future Directions: Recruitment endeavors will continue to guarantee the successful completion of the trial and enrollment goals are expected to be achieved within the proposed timeframe. After completion of the protocol, data analysis will be conducted to determine the short- and long-term effects on pain as well as the behavioral and neurophysiological qualities of responders to this treatment.

Impact: The team's findings will provide targets for improving neuropathic pain levels and minimizing its impairing effects in the SCI population. Their results are expected to have an immediate clinical treatment option and their neurophysiological findings will lay the groundwork for optimization of this state-of-the-art intervention for SCI, thus enhancing their quality of life, participation, and activity levels.

3. 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: SCI-pain is often severe to excruciating, leading to a dramatic decrease in quality of life and increased risks for depression, anxiety, and addiction.

The mechanisms that lead to SCI-pain are poorly understood. This leads to insufficient success in managing SCI-pain, which is often refractory to pharmacological, surgical, and behavioral therapeutic strategies.

A potential cause for the development of SCI-pain is a change in the electrical activity of pain-sensing neurons (nociceptors) induced by the injury. Nociceptors are usually silent in the absence of injury, but become hyperexcitable and spontaneously active following SCI, providing a possible underlying mechanism for the development of chronic neuropathic pain.

Like human patients with SCI, rat models of SCI develop chronic neuropathic pain phenotypes. The goal of this research project is to use for the first time in a rat model of SCI a direct electrophysiological approach to test the core hypothesis that the increased activity of CaV3.2 calcium channels induced by the injury is necessary to drive SCI-nociceptors to a hyperexcitable state and for promoting the development of SCI-pain.

Progress Towards Specific Aims: Preliminary data collected in SCI rats showed an increased incidence of spontaneous activity in SCI-nociceptors in vitro, consistent with a hyperexcitable state of injured nociceptors. Voltage clamp experiments showed that the T-type calcium channels sustain the bulk of the total calcium current active during the interspike interval in spontaneously active SCI-nociceptors, supporting a major role for the T-type calcium channels in driving SCI-nociceptors to a hyperexcitable state.

Behavioral experiments in vivo in SCI rats showed that the SCI-pain could be rescued by treatment with TTA-P2 (a selective blocker of T-type channels). In SCI mice, like SCI rats, the research team's preliminary data showed an increased incidence of spontaneous activity in SCI-nociceptors in vitro, and TTA-P2 rescued the SCI-pain in vivo, providing a strong premise to introduce mice to the project.

Future Directions: The research team's goal is to carry out in vitro electrophysiology experiments in nociceptors isolated from naive, sham, and SCI CaV3.2 mice to determine the contribution of CaV3.2 calcium channels during the interspike interval and to the development/maintenance of SCI-pain.

Impact: Identification of CaV3.2 calcium channel as the key ion channel responsible for the development of SCI-pain will provide a new pharmacological target for reducing SCI-pain and the suffering endured by individuals living with SCI, and for preventing secondary psychological consequences that further reduce their quality of life.

Presentations: Puopolo, M., Kaczocha, M., & Liu, H. *CaV3.2 calcium channels drive nociceptors' hyperexcitability and chronic neuropathic pain following spinal cord injury in mice.* Department of Anesthesiology, Stony Brook Medicine, Stony Brook, Research evening, 2022.

4. 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: SCI damages axonal connections between the spinal cord and brain resulting in a reduction or loss of motor, sensory, and autonomic function below the level of the injury. The initial trauma to the spinal cord also initiates a secondary cascade of pathological processes that leads to further injury and tissue loss, and inflammation is suggested to be one of the key mediators in the progression of the secondary injury cascade. Thus, there is a need to develop, implement, and optimize therapies focused on reducing the extent of SCI-induced inflammation and tissue damage/loss. 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 anti-inflammatory and neuroprotective actions in central nervous system injury/disease.

In SCI, preliminary rodent studies have shown that acute treatment with MIN or PIO decreases multiple processes mediating tissue loss and development of secondary injury, resulting in reduced lesion size and improved hindlimb motor function. Thus, these neuroprotective actions of these agents have high potential for clinical use in SCI, but the efficacy of these agents on SCI-induced bladder (lower urinary tract) and respiratory dysfunction are unknown. This research project is designed to investigate the efficacy and time window of anti-inflammatory and neuroprotective effects of MIN, PIO, and combined MIN/PIO treatment as a pharmacotherapeutic strategy for minimizing secondary injury-related neural tissue damage/loss and promoting improvement of bladder and respiratory function in an adult rat model of acute moderate contusion SCI.

Progress Towards Specific Aims: The research team began experiments evaluating the effects of 7-day MIN (or antibiotic control baytril (BAY)) treatment beginning 24-hr post-SCI on spontaneous recovery of bladder function. Their preliminary data analysis suggests that compared to BAY-treated rats, MIN-treated rats exhibit a slightly greater degree of partial (but not complete) recovery of timing features in awake urination pattern and under anesthesia, reflex micturition behaviors that are characterized by reduced bladder overactivity (e.g., fewer non-voiding bladder contractions) and more efficient voiding contractions.

Future Directions: The team plans to continue their MIN experiments and initiate PIO experiments during the next reporting period.

Impact: This project will provide an effective non-invasive pharmacology-based neuroprotective intervention strategy using currently available FDA-approved agents to improve bladder control, respiratory function, and quality of life in individuals with SCI.

5. The Research Foundation of CUNY obo College of Staten Island
Maria Knikou, P.T., Ph.D.
IDEA: $359,004
Function of Spinal Locomotor Centers During Trans Spinal Stimulation After SCI

Introduction/Background: A critical breakthrough the last decade is the use of transcutaneous spinal cord (or trans spinal) stimulation to improve sensation and movement after SCI in humans. Standing and walking are amongst the most affected tasks after SCI, severely compromising daily living activities resulting also in several detrimental complications. On the other hand, trans spinal stimulation over the thoracolumbar region has been used to improve the ability to stand and walk in these individuals. However, a fundamental knowledge gap still exists on how trans spinal stimulation affects excitability of spinal neurons and leg muscle activity during robotic gait assisted stepping in individuals with motor complete or motor incomplete SCI. This lack of knowledge hinders clinicians and researchers from effectively utilizing trans spinal stimulation during assisted stepping to enable appropriate motor activity and thus walking performance.

Researchers will systematically characterize the effects of trans spinal stimulation on flexor and extensor reflexes, muscle activation patterns, and muscle coordination during robotic gait assisted stepping. These effects will be identified when trans spinal stimulation is delivered above and below motor threshold intensity and at different frequencies (0.1, 50, 100 Hz). Understanding how trans spinal stimulation affects spinal locomotor centers is critical for the development of targeted therapeutic interventions.

Progress Towards Specific Aims: The research team has developed the algorithms needed to treat the electromyography (EMG) artifacts upon 50 or 100 Hz trans spinal stimulation, and the algorithms needed to synchronize EMG with kinematics upon trans spinal stimulation. They successfully completed a methodological study on the most optimal configuration and size of the cathodal electrode for trans spinal stimulation based on the strength of spinal inhibition, electrical thresholds, and recruitment of motoneuron pools.

Future Directions: Dr. Knikou plans to develop, submit, and publish papers with results from the methodological study performed in 11 healthy subjects. She also will schedule and complete experiments in 12 healthy control subjects when trans spinal stimulation is delivered during treadmill walking and its effects are established on EMG and kinematics, and schedule people with SCI for experiments in the next reporting period.

Impact: Results from this research project will advance the field of spinal cord research considerably and change the standard of care because there is great potential for development of novel and effective rehabilitation strategies to improve leg motor function after SCI in humans.

6. 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 their posture while sitting, performing these common daily tasks could be highly demanding, or even impossible. Particularly, it is a challenge for those with a spinal cord lesion in the cervical or high-thoracic regions of the spine.

Recently, the Robotics and Rehabilitation (ROAR) Laboratory at Columbia University has developed a novel Wheelchair Robot for Active Postural Support (WRAPS). The system offers the following capabilities: it can dynamically assist the trunk during reaching movements when sitting in a wheelchair by either controlling the position of the trunk or by applying external forces to it; and it can be programmed to modify trunk posture of the subject to indirectly affect the base of support (BOS) and reduce pressure build-up between gluteal area and the wheelchair seat. The research team will assess the effects of dynamic assistance provided by WRAPS on wheelchair users with severe SCI to facilitate static/dynamic postural control, reaching activities, and control of under-seat pressure.

Progress Towards Specific Aims: The research team has 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 (3) rotational degrees-of-freedom (DOFs). The end-effector translation is also coupled with the rotation to accommodate the natural movement of the pelvis on the seat. The device was tested with seven (7) healthy subjects to evaluate the workspace provided by the device compared to their natural range of motion (ROM). The position accuracy of the device was also validated against a virtual reality (VR) motion tracking system. The development of pWRAPS, validation of the system, and preliminary characterization with healthy subjects are critical steps to test on people with SCI.

Future Directions: A force control architecture has been developed and is currently being tested with pWRAPS. The features of this force controller will be tested within the scientific aims of the proposal. A validation study will first be performed with healthy subjects and soon after it will be adapted for individuals with SCI.

Although the Research Assistant’s work to identify and screen potential participants at Helen Hayes Hospital has been delayed due to the pandemic, the team expects that these efforts will resume soon. In the meanwhile, the design of the robotic device and testing is being carried out at Columbia University as per the project schedule.

Impact: Results are expected to have a significant impact on the functional activity and quality of life of people with SCI who are in wheelchairs. This is the first time a wheelchair robot has been developed for wheelchair users, specifically for those with SCI. pWRAPS will be investigated in the context of assistance and training of upper body movements during functional tasks. pWRAPS will promote independence in people with cervical or high-thoracic SCI. Moreover, pWRAPS will offer a safer environment to avoid excessive gluteal pressure build-up during wheelchair use via pelvic-trunk movements. This will help maintain cardiovascular status and protect against skin breakdown of the users.

Presentations: Ophaswongse, C., Lent, V. and Agrawal, S.K. *Kinematic Validation of a Robotic Exoskeleton for Assisting Seated Pelvic Movements by Wheelchair Users with Trunk Impairments*. The 9th IEEE RAS/EMBS International Conference on Biomedical Robotics and Biomechatronics, Seoul, Korea, August 21-24, 2022.

7. Winifred Burke Medical Research Institute

Yutaka Yoshida, Ph.D.
IDEA: $360,000
Modulation of Presynaptic Partners of Corticospinal Neurons to Improve Motor Recovery After Spinal Cord Injury

Introduction/Background: In humans, corticospinal (CS) neurons play a major role in controlling voluntary movements. Therefore, injured CS neurons by SCI often causes permanent paralysis in humans. Previous studies have mainly focused on determining how to promote regeneration of injured CS axons within the spinal cord after SCI. However, in addition to sending signals through their axons, CS neurons receive inputs from pre-synaptic neurons (pre-CS neurons) in the brain through their dendrites. It remains unknown how connectivity between pre-CS neurons and CS neurons is influenced upon SCI, because pre-CS neurons have not been carefully identified. Moreover, it is unknown whether simultaneous stimulation of both pre-CS neurons and CS neurons is more efficient to enhance axon regeneration and motor recovery than only CS neuron stimulation after SCI. Thus, there is a critical need to understand how connectivity between pre-CS neurons and CS neurons is altered after SCI, whether the connectivity is influenced by cortical stimulation, and simultaneous stimulation of both pre-CS neurons and CS neurons is more efficient to promote axon regeneration and motor recovery than only cortical stimulation after SCI.

The goal of this study is to develop a novel strategy to promote CS connectivity and motor recovery after SCI. Our overall objectives of this application are to test our central hypothesis that connectivity between pre-CS neurons and CS neurons is altered after SCI, cortical stimulation alters connectivity between pre-CS neurons and CS neurons after SCI, and simultaneous stimulation of CS neurons and pre-CS layer V (specifically Va) neurons enhances axon regeneration and motor recovery after SCI.

Progress Towards Specific Aims: The research team has established the dorsal hemi section model at cervical levels. They are also in the process of setting up optogenetic activation of layer Va neurons.

Future Directions: During the next period, the research team will perform rabies virus assays before and after SCI. Then they will perform anatomical analyses.

Impact: Determining how connectivity between pre-CS neurons and CS neurons is altered after SCI with or without cortical stimulation will provide new opportunities for development of a novel therapy for SCI patients in humans.

8. 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: SCI often causes permanent paralysis due to failure of injured corticospinal (CS) axons to regenerate. 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 research team plans to develop a novel strategy to promote regeneration of corticospinal neurons (CSNs) and motor recovery after SCI.

The central hypothesis of their 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 their combined strategy after SCI in mice will provide new opportunities for development of novel therapy for SCI patients in humans.

Progress Towards Specific Aims: The research team have accomplished establishing the contusion model of SCI at cervical levels. The team is also in the process of setting up stimulation of Chx10+ spinal interneurons by optogenetics.

Future Directions: During the next period, the team will perform Chx10+ spinal interneurons after SCI and then will be able to determine injured CS axons and skilled motor behaviors.

Impact: The research team 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 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.

Progress Reporting Period
11/01/2021-04/30/2022

7 Awards (3 PART, 4 IDEA awards previously concluded), Procurement Total: $4,198,058

1. **Bronx Veterans Medical Research Foundation, Inc.**
   Dr. Christopher Cardozo; Formerly William A. Bauman, M.D.
   PART: $826,939
   Treatment with Romosozumab versus Denosumab to Improve Bone Mineral Density and Architecture in Subacute SCI.

   Introduction/Background: Persons with SCI lose substantial amounts of bone below the level of injury, predisposing them to fracture. With the advent of robotic exoskeletal-assisted devices, direct stimulation of the spinal cord (epidural stimulation), and the future possibility of repairing the connections in the spinal cord to permit walking, it is of obvious clinical relevance to have bones of the leg that remain strong enough to bear the body's weight while walking without fracture. To date, there has been no literature on the successful prevention of bone loss at the knee in persons with SCI. The knee is the skeletal site where most persons immobilized by SCI will suffer a fracture, and the risk of fracture walking is considerably greater than that of sitting in a wheelchair.

   Progress towards specific aims: A total of 13 potential participants with subacute SCI were screened for participation. From these 13 individuals, two (2) additional participants have been enrolled in the study. Three (3) participants are currently enrolled and ongoing in the study. Several potential participants with subacute SCI at the James J. Peters VA Medical Center and Kessler Institute for Rehabilitation sites are in the process of being screened for study enrollment.

   Future Directions: To compete the study within the one-year NCE, the original study will be shortened to compare the administration of romosozumab versus denosumab on distal femoral areal bone mineral density over 12 months, which is the objective that has most clinical relevance in the original protocol.

   Impact: To prevent osteoporosis, which is important to health, wellbeing, and independence of persons with chronic SCI.

2. **Winifred Masterson Burke Medical Research Institute**
   Edmund R. Hollis, Ph.D.
   PART: $963,000
   Rehabilitation and Cortical Remodeling After Surgical Intervention for Spinal Cord Injury

   Introduction/Background: Upper extremity nerve transfer surgery is a state-of-the-art intervention for individuals with mid to low cervical injury; however, functional outcomes after surgery have been highly variable, to date. The research team aims to evaluate the physiological and functional outcomes promoted by intensive rehabilitation in individuals that undergo nerve transfer surgery. Outcomes as well as

underlying neurophysiological changes will be tracked in humans, with parallel experiments in an established pre-clinical mouse model.

Progress towards specific aims: The research team has completed robot-assisted training on one participant. Five (5) individuals were enrolled in the study prior to COVID-related restrictions. These individuals underwent baseline, pre-surgery testing as outlined in earlier reports. Due to time constraints, the research team reopened enrollment for individuals that have already undergone nerve transfer procedure and whose one-year post-surgery date falls within their funding period. Four (4) individuals have been enrolled after undergoing nerve transfer surgery. These individuals have not yet undergone rehabilitative training at Burke Neurological Institute.

The research team has demonstrated that refining their pre-clinical approach to include electrical stimulation conditioning to enhance the regenerative response in mice improves regeneration of the axons required for movement. Furthermore, they have found that this enhanced regeneration improves physiological outcomes in mice with chronic SCI. Further assessment of histological and functional outcomes is ongoing.

Future Directions: The research team anticipates that at least two (2) individuals will have completed robot-assisted rehabilitation. Also, they are processing histological sections and analyzing data in chronically injured mice that received enhanced nerve transfer surgery.

Impact: The research team anticipates that mapping brain changes with post-surgical recovery and intensive motor training will show brain reorganization associated with re-innervation and functional recovery from training. Both the human and animal arms of the study will provide complementary and supporting evidence. Furthermore, the pre-clinical model will allow a more specific evaluation of physiological changes in the brain that underlie recovery; while the human study will determine potential physiological biomarkers for recovery and test the feasibility of intensive rehabilitation around the time of functional re-innervation.

3. Winifred Masterson Burke Medical Research Institute
Jian Zhong, Ph.D.
PART: $990,000
Repetitive Transcranial Magnetic Stimulation (rTMS) As a Means to Promote Corticospinal Tract (CST) Axon Regeneration

Introduction/Background: Recently, evidence has accumulated that a relatively simple method of brain stimulation, rTMS, can slightly improve some symptoms of paralysis. The research team will use mouse models of SCI to investigate what mechanisms are activated by rTMS treatment that could lead to improved nerve function, and how much improvement may be possible using rTMS alone or in combination with other interventions. Their preliminary data suggest that rTMS can activate RAF-MEK signaling, an intracellular mechanism that can drive axon growth and regeneration. Finally, the team will treat a group of volunteer SCI patients with rTMS to see how well they tolerate the therapy while participating in a rehabilitation

program. Progress towards specific aims: We have completed the planned experiments and identified a set of transcription factors (TFs) activated by B-RAF GOF in mature CSNs that substantially overlaps with the set of TFs induced in axotomized zebrafish retina ganglion cells (RGCs). Zebrafish RGC can regenerate their axons after an optic nerve injury, restoring visual function. Furthermore, high-frequency repetitive (HF-r)TMS treatment regulates the same set of TFs in a similar manner as B-RAF activation. Thus, our results reveal a core mechanism of how axon regeneration can be triggered in CSNs. Moreover, we performed TRAP-seq analysis of PTEN LOF CSNs and found that they regulate a very different set of transcripts. Combined activation of the RAF - MEK and PTEN - mTOR pathways should therefore additively boost CST axon regeneration. However, we were not able to detect any enhanced axon regeneration or sprouting in combined B-RAF GOF / PTEN LOF mice, or in PTEN LOF mice treated with HF-rTMS, compared to the effects we documented in B-RAF GOF mice, or wild-type HF-rTMS treated mice.

We presented part of our results at the March 2022 Gordon Research Conference “Central Nervous System Injury and Repair” in San Diego.

A manuscript describing the B-RAF GOF and HF-rTMS in promoting axon growth was published online (*https://www.biorxiv.org/content/10.1101/2022.06.01.494346v1.full*), while under review at Sci Transl Med. A revised version of the manuscript has been re-submitted to Sci Transl Med.

We have performed a new 3-photon calcium imaging experiment in Ithaca in April 2022 (due to COVID19 restrictions, animal transfer to Ithaca was prohibited until Feb. 2022). We planned another experiment for June 2022; however, this was cancelled due to the impending closure of my laboratory (see below).
Dr. Xiaofei Guan presented the Ca imaging results at the March 2022 Gordon Research Conference “Central Nervous System Injury and Repair” in San Diego.
As a result of the COVID19 pandemic, the number of new SCI patients dropped dramatically during 2020-21. We therefore switched from our original plan to test the HF-rTMS protocol with subacute SCI patients to chronic SCI patients. In the three chronic SCI patients treated with HF-rTMS at 120% of RMT intensity, two tolerated the treatment well while one reported modest headache. This same patient showed improvement in hand function at the post-test evaluation following the 15 treatment sessions (**Fig. 1**). Our initial results, from able-bodied volunteers (all of whom tolerated the treatment well) and SCI patients, are either published or accepted for publication; see below.

The advantage of this combination of animal study and human treatment is that we can observe what happens in patients, and if problems arise go back to the mice to try out modified treatment protocols. To minimize side effects, we test applying HF-rTMS directly to the spinal cord instead of the brain. We are collaborating with a biomedical engineering group at NIH, led by Dr. Hanbing Lu, who have built a small coil (#2021sx) that allows us to deliver strong magnetic stimulation more focally than the commercially available coils. We have recently begun using this coil to administer

spinal HF-rTMS to our unilateral pyramidotomy (uPx)-lesioned mice. The first set of data looks promising, with substantial sprouting of new collaterals into the denervated side of the CST.

Future Directions: The researchers' aims to develop a novel treatment strategy for SCI patients by translating the findings obtained from animal models to human clinical practice are expected to fill the current gap in knowledge as to whether non-invasive brain stimulation via rTMS could be a promising route toward axon regeneration after SCI. If successful, the team will collaborate with rehabilitation hospitals to test to which extent rTMS can be used to improve axon regeneration and neurological outcomes in SCI patients. The research program will continue at the Kessler Rehabilitation Institute with their own internal funding.

Impact: Mechanism-based strategies are sought for the development of clinically applicable therapies that could enable functionally meaningful recovery after spinal cord injury. Despite recent progress in identifying intrinsic and extrinsic players in regulating CNS axon regeneration and advances in the development of sophisticated repair strategies, the goal of functionally meaningful and clinically translatable spinal cord regeneration remains unfulfilled. If we can achieve substantial axon regeneration and walking recovery in our mouse models with rTMS alone or in combination with genetic activation of other growth-associated pathways, and if the rTMS treatment is well-tolerated by the patients, we will have laid a firm basis for the development of new treatment strategies for SCI patients, in line with the goal of the RFA to foster the translation of results from basic (preclinical) research into the next research phase If the researchers' aims are successful, they will have laid a firm basis for the development of new treatment strategies for SCI patients, in line with the goal of the RFA to foster the translation of results from basic (preclinical) research into the next research phase.

Individual Predoctoral and Postdoctoral Fellowships (Round 5)
Contract Term 10/01/2023-09/30/2026

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

1. **Winifred Burke Medical Research Institute**
   Yutaka Yoshida, Ph.D. and Alzahraa Amer, Ph.D.
   Postdoctoral: $180,581
   Restoration of Motor Function Following SCI Via Optical Stimulation

   Introduction/Background: The limited recovery of mobility following spinal cord injury (SCI) has inspired a significant amount of research aimed at repairing the injured spinal cord. Neuromodulation-based therapies can promote integration of connections between the brain and the spinal cord after injury into functional circuits, and in this way, help to restore a certain degree of motor function.

Optogenetics can provide real-time, selective control of neuronal activity to modulate behavior. In this proposal we aim to leverage opsins with ultra-high light sensitivity and wireless optogenetic spinal interface technology to achieve robust motor recovery in a preclinical model of cervical contusion injury. It has been demonstrated that after SCI, the severed descending axons can form new synapses on surviving propriospinal neurons (PNs). These PNs axons, travel in the ventral and lateral white matter and are therefore spared by most incomplete contusive injuries.

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

Introduction/Background: Spinal cord injury (SCI) affects close to 500 000 people globally every year, with the most common being incomplete cervical injuries. These injuries spare some descending motor circuits, and an important repair strategy is to target these spared connections through activity-dependent plasticity. Knowing which pathways mediate dexterity in health and injury remains a key gap in our understanding and is critical for developing a substantial treatment. We hypothesize that the cortico-reticulospinal pathway is important for forelimb motor function, both in health and after injury. This hypothesis is based on experiments in rodents and humans showing the adaptive role of this system after injury, and we predict that it is important in health as well.

The first aim of this proposal is to determine the necessity of this pathway in dexterity. We will accomplish this by reversible chemogenetic inhibition via DREADDS (Designer Receptors Exclusively Activated by Designer Drugs) of the projection first in healthy rats, then again after an incomplete cervical spinal cord injury in the same rats. Thus, with each rat acting as its own control, we will be able to determine the contribution of this pathway to fine motor function in an important model system. Our analysis will be focused on the behavioral, physiological, and anatomical correlates of this inhibition. Our prediction is that transient inhibition of the Corticoreticular pathway will lead to significant deficits in fine motor control of healthy animals; furthermore, after injury, functional recovery will be abrogated with inhibition of the same circuits.

The second goal is to test the sufficiency of Corticoreticular connections to improve function after SCI. To do this, we will use viral insertion of a light-sensitive channel into these connections and optically stimulate the fibers repeatedly. Specifically, we will inject a cre-dependent excitatory opsin packaged into an adeno-associated virus (AAV) in the motor cortex and inject a retrograde AAV constitutively expressing cre in the medullary reticular formation. By repeated activation of these projections and their downstream circuits, we strive to permanently strengthen the neural circuits which are necessary for fine motor function. We will perform stimulation 30 minutes a day for each of ten days after injury in our intervention group and compare the changes in the same three outcomes relative to a group which does not receive stimulation. The primary outcome measure is a test of forelimb reaching, and we will also perform comprehensive anatomical, physiological, and behavioral validation. We expect rats that receive optical stimulation to outperform the sham-stimulation controls.

Finally, the career development program designed with the fellowship will bridge the training gap from my current position, a new postdoctoral scientist, to a tenure-track position in academia specializing in spinal cord injury. The first two development goals are directly related to the scientific work in this proposal, and the final development goal is a composite which will enhance my scientific communication skills, computational ability, and leadership/career independence, all complementary skillsets which are essential for doing exceptional work.

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

Introduction/Background: The corticospinal system is essential for movements in humans and many animals. Damage to this system causes weakness and paralysis. The corticospinal system is comprised of the motor cortex, where movements are initiated, and the corticospinal tract, which is the direct link between the motor cortex and the spinal cord circuits that produce movements. Spinal cord injury (SCI) disconnects the motor cortex from the motor circuits in the cervical enlargement that integrate descending and proprioceptive afferent signals to produce upper/forelimb movements. For muscle activation, the CST in all species engages spinal interneurons, especially premotor interneurons and, additionally in humans and some non-human primates, motoneurons directly. Most SCIs are incomplete. After incomplete injuries that severely damage the CST, the motor cortex can continue to contribute to movement control via indirect pathways to the spinal cord, such as the cortico-reticulospinal path. The research focus of this proposal is to promote motor function after SCI. To do this requires a better understanding of the pathophysiological events contributing to impaired motor functions and to devise interventions to ameliorate those events.

Selective lesion of the corticospinal tract in the medulla results in a substantial loss of downstream spinal cord premotor interneurons in the cervical enlargement and their synapses on motoneurons; termed trans neuronal degeneration. Inactivation of the motor cortex produces a similar loss of these premotor interneurons and their synapses, demonstrating an activity-dependence to this degeneration. We previously showed that supplementing spinal cord activity after CST lesion using cathodal trans spinal direct current stimulation (c-tsDCS) protected the interneurons from trans neuronal degeneration. The overall aim of this application is preserving motor circuit integrity caudal to a C4 SCI. In the two aims, we will tackle the problem of trans neuronal degeneration of premotor interneurons after SCI using neuromodulatory approaches. In Aim 1 we will determine the effect of c-tsDCS after cervical SCI on microglial activation and the persistence of interneuron survival after completing the therapy. We will critically examine trans neuronal premotor interneuron degeneration in the context of a preclinical SCI model. To translate to therapy, we will determine if spinal neuromodulation produces persistent protection of premotor neurons from trans neuronal degeneration. To elucidate mechanism, we will determine the effect of c-tsDCS on microglial engulfment of spinal interneurons and on potential trigger signals that drive engulfment.

After severe SCI, CST projections to segmental premotor circuits are largely lost. In Aim 2, we ask if chronic motor cortex neuromodulation recruits indirect spinal

pathways to abrogate spinal neuron trans neuronal degeneration after cervical SCI. We will determine how motor cortex neuromodulation after SCI can provide a surrogate source of spinal activity to protect premotor interneurons from trans neuronal degeneration, not through direct segmental CST activation but indirectly by activation of propriospinal neurons and brain stem motor pathways. We will also determine how a strong plasticity-promoting neuromodulation protocol, motor cortex theta burst stimulation (TBS), can provide persistent neuroprotection alone and in combination with cathodal-tsDCS.

Trans neuronal degeneration likely contributes to loss of motor functions after SCI because premotor interneurons are essential elements in spinal movement control circuits. Importantly, trans neuronal degeneration could limit recovery after SCI. Now that we know that trans neuronal degeneration of spinal premotor interneurons occurs after injury, it is imperative to develop ways to intervene to prevent this loss and preserve the integrity of spinal circuits below an SCI. Successful completion of this project will advance the translation of a novel neuromodulation strategy for maintaining spinal motor circuit integrity.

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

   Introduction/Background: Following spinal cord injury, the loss of ionic homeostasis and large increases in intracellular calcium concentrations through hyperactivation of AMPA and NMDA receptors prevents leads to cell death, preventing neuronal recovery and regeneration. Gabapentin, an FDA-approved compound for neuropathic pain, blocks the α2δ2 subunit of voltage-gated calcium channels. Through studies utilizing systemic delivery of gabapentin, it has shown to inhibit NMDA receptor-activated ion currents, providing neuroprotection, as well as promoting sprouting of neurons. Oral administration of small molecule drugs requires high and potentially harmful doses, and often cannot penetrate the blood-brain barrier once it reforms. Furthermore, systemic administration of gabapentin can lead to addiction, therefore it is crucial that a local delivery system is developed. In this proposal, I aim to develop a novel poly(pro-gabapentin) polymer that is capable of releasing gabapentin over several months. The polymer will consist of gabapentin covalently linked to a HEMA backbone, allowing for controlled concentrations of gabapentin loading. Furthermore, the polymer will be created into subdurally implantable films, where the neurotrophic and neuroprotective effects will be tested with dorsal root ganglia neurons in vitro. I hypothesize that the poly(pro-gabapentin) polymer will be protect affected neurons from excitotoxicity and will promote increased sprouting and neurite outgrowth, through use of local, sustained delivery. The in vitro testing described in this proposal integrates physiologically relevant aspects of SCI to accurately assess the protective and regenerative capacity of the poly(pro-gabapentin) films for future in vivo studies.

5. **Columbia University**
   Sunil K. Agrawal, Ph.D. and Priya Kulkarni
   Predoctoral: $116,000

Improving Trunk and Neck Coordination During Reaching Tasks with a Robotic Neck Brace in Individuals with Spinal Cord Injury

Introduction/Background: In patients with spinal cord injury head, neck control as well as postural stability have been found to be a limitation in their movement ability. Unfortunately, there is limited research into the coordination of head and trunk during seated postural tasks in patients with SCI. There are also no strategies for helping patients with SCI regain their head and trunk coordination during these tasks.

The proposed project uses a robotic neck brace, which has been designed and validated in our lab. This brace has been used in studies with healthy subjects, ALS patients, cervical spondylosis patients, children with cerebral palsy, and patients with cervical dystonia.

A group of 15 healthy subjects will be recruited to complete a set of seated reaching tasks. They will be asked to reach forward, laterally, and diagonally with each of their hands to press a buzzer. While they complete these tasks, several markers will be placed on their torso, so that their trunk motion can be captured by motion capture cameras. They will also be wearing the neck brace, which will record their head and neck movement during the reaching tasks. The data collected from these tasks will be synced and the coordination between the trunk and neck motion will be analyzed.

A mapping function will be developed for head and trunk coordination after the characterization study of healthy subjects. Using regressions and validated statistical methods, I will create a model that can accurately predict the position of the head based on the position of the trunk.

A novel force field will be developed which can be centered anywhere in the workspace of the head. This force field will be set up as a cone, where the brace will direct the head to a specified position. The magnitude of the force applied to the head will scale with the distance from the desired position. The position of the force field will be based on real-time data from the user. Based on the position of the trunk, the expected head position will be predicted and sent to the brace.

Fifteen SCI patients with injuries in the high thoracic and cervical region of the spinal cord will be recruited for this experiment. They will complete the same reaching task as the group of healthy subjects. However, they will complete the task under two conditions, one with the neck brace force field turned off, and one with the force field on. We will compare the deviation of the trunk from a straight line during each of these conditions. We hypothesize that the trunk motion will be more stable with smoother motion during the condition with the force field.

This project will have two main goals: (i) Create a control strategy to coordinate head and trunk motion using the robotic neck brace. Using a variable force field and a visual feedback program, create a mapping function between the head and trunk motion. (ii) Recruit 15 SCI patients to complete reaching tasks with and without the force field, with the goal of assisting their head control during reaching tasks. Accomplishing these aims would advance treatment and rehabilitation of chronic or acute SCI.

6. Icahn School of Medicine at Mount Sinai

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

Introduction/Background: Despite myriad advances in the treatment of Spinal Cord Injuries (SCI), such as functional recovery with physical therapy, individuals with SCI rarely achieve full mobility or the ability to stand unassisted. Excitotoxicity and an inhibitory environment, in addition to the initial damage to blood vessels, neuron cell membranes, and axons prevent functional recovery from SCI. Likewise, never conduction in the Cortico-Spinal Tract (CST), which is an effective measure of function, is reduced. Physical training improves the functional outcome of patients with SCI, potentially through the recruitment of surviving neurons. However, there remains a distinct lack of drugs or therapies that promote axonal regeneration after SCI. There is a critical need for pharmaceutical interventions need to be developed to promote axonal regeneration and improve the recovery associated with physical therapy. Our lab has developed drug therapies that improve mice's Basso, Beattie, and Bresnahan (BBB) Scale scores and/or promote axonal regeneration in the retina. The goal of this research proposal is to reproduce these results in the CST of rats, which show cavitation unlike mice and to identify the mechanism of action of one of these drugs while developing electrophysiological procedures that will be used to record CST potentials in awake, freely moving rats.

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

Introduction/Background: Postural control is an integral part of daily living for wheelchair users. The ability to remain stable in an upright sitting position and return to this body position after performing a dynamic movement is an essential skill to achieve and maintain throughout their lives. However, people with spine injury lack synergistic control of key postural muscles as well as sensory inputs, which results in poor voluntary trunk control and movement compensation by non-postural muscles. Our Wheelchair Robot for Active Postural Support (WRAPS) can directly manipulate the pelvic and the thoracic segments of the user by applying forces and moments on each of the segments. The system can be integrated with other kinematic sensors (IMUs, VR trackers) to obtain information about upper limb movements during functional tasks.

My three research aims are as follows: (I) to characterize effects of postural training provided by WRAPS to healthy subjects in different force and visual feedback conditions; (II) to investigate training effects provided by WRAPS like Aim (I) on SCI patients with partial trunk impairment, and (III) to develop an intuitive user-intent control interface in the WRAPS for patients who severely lack trunk control.

Our first and second aims are to use the WRAPS to train seated functional movement, promote healthy sitting posture, and enhance sitting stability of individuals with SCI who have partial trunk control. Using WRAPS, we will explore different training methodologies and ways to quantify the improvement of one's control of posture using different physiological sensor modules, e.g., motion capture,

surface EMG, and non-invasive EEG. The third aim is geared towards population with higher levels of impairment where the WRAPS is mainly used to restore and augment daily functional movement of the user through force assistance at the pelvic and the thoracic levels. Algorithms for user-intent based controllers of the WRAPS will be developed from collected physiological data associated with postural movements.

8. Cornell University

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

Introduction/Background: Traumatic insult to the spinal cord injury (SCI) is a devastating medical problem. In United States alone thousands of people suffer from these injuries leading to complete paralysis. SCI not only causes severe physical damage to humans, but also causes substantial psychological, social, and financial burden to the world population. After the primary insult to the spinal cord, a secondary injury is rapidly initiated causing the death of neurons, glial cells, activation of inflammatory cells, ischemia leading to tissue death. Additionally, after the insult, reactive astrocytes are activated leading to the formation of growth inhibitory molecules and glial scar tissue formation. Currently, there is not an effective treatment for people suffering from SCI. Therefore, there is an urgent need to continue to improve and develop new therapies to treat SCI.

After insult to the spinal cord, mammals do not naturally recover neural tissue, leading to damaged tissue and permanent loss of function. Lower vertebrates such as fish have the capacity to regenerate their tissue after injury. Our lab has been exploring the regenerative capabilities of goldfish and the composition of their extracellular matrix (ECM). We found that goldfish regenerate their spinal cord within 5-7 weeks post-injury. The composition of regenerative goldfish ECM remains largely unexplored. Therefore, to help improve repair and recovery after spinal cord injury (SCI), I propose a combination of an injectable hydrogel and a stabilized enzyme to overcome neuron loss and promote axonal growth. This therapy will consist of a 1) hydrogel produced from regenerating goldfish extracellular matrix (ECM) and a coacervated Chondroitinase ABC (ChABC). I will obtain, decellularize, and characterize goldfish and mouse ECM for in vitro studies. With the help of liquid-chromatography mass spectrometry, I will be able to determine when goldfish produce regenerating ECM (rgECM). This rgECM will be used to produce the hydrogel to be used in vitro studies to examine how it provide a growth permissive environment for axons to regrow. 2) I will fabricate a coacervated ChABC, this will produce a stabilized ChABC enzyme that will degrade Chondroitin Sulfate Proteoglycans (CSPGs) leading to the reduction of glial scarring tissue formation. After in vitro testing, I will examine the effects of this therapy in vivo; examine how it affects tissue regeneration and functional recover.

Individual Predoctoral and Postdoctoral Fellowships (Round 4)
Contract Term 08/01/2019-07/31/2022

Progress Reporting Period
08/01/2021-01/31/2022

5 Awards, Procurement Total: $1,162,694

1. Columbia University

Sunil K. Agrawal, Ph.D. and Tatiana D. Luna, M.S.
Predoc: $135,600
Improving Upper Body Trunk Control in Spinal Cord Injury Patients Through Robotic Rehabilitation Training

Introduction/Background: The Robotics and Rehabilitation (ROAR) Lab has previously developed a robotic Trunk Support Trainer (TruST) and a Robotic Upright Stand Trainer, (RobUST). These cable driven devices can provide assistive and resistive forces to the participant at the level of the trunk. One of the main goals of this project is to explore the assistive contributions these robotic devices can make in training SCI participants to regain trunk control in standing, seated, and transitioning from sit-to-stand.

Progress towards specific aims: The research team characterized trunk control with TruST in SCI participants to evaluate the potential use of TruST as a training/ rehabilitation device. To accomplish this, the research team brought in five (5) SCI participants with a neurological SCI level ranging from the fourth to the eleventh thoracic vertebrae (T4-T11). Using a video motion capture system, they characterized the participants' seated trunk range of motion with and without the support of the robotic device TruST. They observed in one session, that with the use of TruST, participants showed a greater ability to increase their active seated trunk workspace.

The research team also investigated the potential of cable driven robotics in conjunction with an intensive postural training based on motor learning and control principles to maximize sitting independence. Ten (10) able bodied participants completed a postural standing experiment using RobUST and compared their postural balance reactions with the assistance of the cable robotic device versus assistance from a traditional handrail support. They observed that participants with assistive forces from RobUST enhances postural balance without significantly removing muscular control mechanisms that are of interest in re-training postural control strategies in standing, nor decreasing ground reaction force distribution. They also investigated how participants motion is altered with a load on the pelvis during squatting, a common intervention prescribed to improve sit-to-stand.

Future Directions: The team's results show the potential to use cable driven robotic platforms as training devices to expand seated and standing workspace for individuals with SCI. Next, a training pilot study will be implemented. The cable

robotic device has several functionalities and could be further tested to assist in creating a training paradigm.

Impact: This is the first time TruST has been used as a tool to assess the active seated workspace of individuals with thoracic-lumber SCI. The team's results demonstrate that TruST can expand the seated workspace area and increase the active trunk's excursion of individuals with SCI.

Also, pelvic assistive forces from RobUST allowed participants to have similar postural center of pressure outcomes as holding a handrail, but without significantly removing muscular control mechanisms that are of interest in re-training postural control strategies in standing, nor decreasing ground reaction force distribution. The pelvic support via RobUST also decreased postural excursions for all perturbation directions.

Publications: Santamaria, S., Luna, T.D., Agrawal, S.K. (2021). Feasibility and Tolerance of a Robotic Postural Training to Improve Standing in a Person with Ambulatory Spinal Cord Injury. *Nature: Spinal Cord Series and Cases*, 7, 94.

2. Icahn School of Medicine at Mount Sinai

Ann M. Spungen, Ed.D. and Chung-Ying Tsai, Ph.D.
Postdoc: $189,476
The Effects of Incorporated Exoskeletal-Assisted Walking in SCI Acute Inpatient Rehabilitation

Introduction/Background: The potential functional and health benefits of exoskeletal-assisted walking (EAW) have been demonstrated in persons with chronic SCI. However, few studies have been published that have an EAW intervention for persons with SCI during acute inpatient rehabilitation (AIR). The research team will test the effect of early incorporated EAW training in AIR on accelerating functional recovery and reducing pain and inflammation.

Progress towards specific aims: Although the COVID-19 pandemic delayed the participant enrollment progress, the research team enrolled 27 participants. 24 participants have completed the study (attrition rate is 11%), three (3) of the 27 withdrew from the study for various reasons. 14 and 10 participants were assigned to the EAW group and the control group, respectively. The preliminary results show that the EAW group compared to the AIR only group had significantly better improvement in the total motor score. There is a trend that the EAW group could have better improvement on the lower extremity motor score and sub-score of respiration and sphincter management from spinal cord independence measure.

Future Directions: The research team will continue to enroll participants and try to achieve the enrollment goal within the project period. The fellow will continue to develop skills to establish a solid foundation in SCI research. The fellow has submitted a NIH R01 and will be submitting a NIH R03 using the preliminary data from this study.

Impact: If the study results demonstrate that AIR with EAW training can improve functional independence better than AIR standard of care for people with SCI, this would serve clinicians and clinical practice guidelines as an important reference for including EAW into the standard of care for inpatients during acute and subacute SCI rehabilitation.

3. New York University School of Medicine

Dan R. Littman, M.D., Ph.D. and Hyeon Kyu (Alice) Kwon, B.S.
Predoc: $135,600
Enteric Glial Cells Cause Gastrointestinal Complications Post Spinal Cord Injury

Introduction/Background: The project is to define the cellular pathways involved in gastrointestinal (GI) complications post SCI. Homeostasis is disrupted in the intestinal compartment of SCI patients; however, very little is known about the cause of such disruption and the resulting GI complications when the complications can drastically impact the patients' quality of life. Many recent studies show enteric nervous systems as crucial part of intestinal homeostasis, so the fellow aims to characterize and investigate the role enteric glial cells (EGCs) in keeping intestinal homeostasis as well as microbiome.

Progress towards specific aims: The fellow has made a novel mouse line with a deletion of LTF, Lactoferrin, specifically from the EGC and validated the mouse using fluorescent imaging. They found that protein is no longer expressed in the colonic EGCs. Although the mouse's physical condition and hematoxylin and eosin (H&E) staining revealed there is no major deficit, preliminary results indicate changes in the goblet cell numbers and pH of mucus produced by goblets in the absence of LTF in colon.

Future Directions: The fellow is collecting fecal samples to study the difference in microbiome composition of mice with impaired LTF. Furthermore, they will perform RNA sequencing to understand the differences in the epithelial layers of the colon in the absence of LTF, to further their knowledge of how the barrier function is impaired when the EGCs lack LTF.

Impact: This is the first dataset characterizing the EGCs from colon during homeostasis along with validation on protein level. LTF is an antimicrobial peptide that sequesters free iron which is crucial to bacterial growth, so it's specificity to EGCs in the GI tract is intriguing. Also, possibility that glial cells may interact with intestinal epithelial cells to regulate mucosal health is a novel function of glial cells. Finally, as astrocytes of the brain do not express LTF, this may be used as tool to manipulate the EGCs and study their functions without perturbing the astrocytes in the future.

4. Regenerative Research Foundation

Sally Temple, Ph.D. and Elizabeth Fisher, Ph.D.

Postdoc: $184,686
Modulation of Inflammation Following SCI Using Plasmid IL-10 Microbeads

Introduction/Background: Infiltration of immune cells into the spinal cord (SC) following injury exacerbates initial damage, resulting in neuronal death and poor patient outcomes. The inflammatory cascade post-SCI is well characterized, and now, single cell analysis enables a deeper understanding of how treatments can modify the inflammatory response. The researchers' goal is to treat injured SC with Interleukin-10 (IL10) plasmid DNA beads (IL10pDNA) to modulate immune cells to reduce damage and promote repair. IL10 is a known anti-inflammatory cytokine primarily targeting microglia and macrophages, key regulators of immune activation in the SC. They will compare the effect of treatment at the single cell level. These experiments will enable identification of novel pathways impacting injury recovery.

Progress towards specific aims: The research team has made progress through immunohistochemical analysis of tissue for cell types as in vivo confirmation of flow cytometry findings. They also made progress through the identification of potential pathways in which IL10 may be targeting microglial cells following injury. Single nuclear RNA sequencing was performed; however, low quality of samples did not allow for analysis.

Future Directions: The fellow plans to complete sectioning of harvested spinal cords and analyze tissue for the immune cell populations present at three (3) and seven (7) days post injury, for control vs IL10pDNA beads. They also plan to perform the injury and collect one (1) and 14-day timepoints to perform flow cytometry, collecting the tissue for histological analysis. They will perform SCI surgeries for all timepoints to collect for single cell analysis.

Impact: After completing this study the researchers will have discovered the effects of IL10pDNA beads on immune cell subpopulations at key times after injury, and their gene expression at the single-cell level, providing insights into novel pathways for regulating immune cell infiltration following SCI.

5. **University of Rochester Medical Center**
Bradford C. Berk, M.D., Ph.D. and Chia Hsu, Ph.D.
Postdoc: $189,366
The Role of Phosphodiesterase 10A in Inflammation After Spinal Cord Injury

Introduction/Background: The objective of this project is to test TP-10 as a novel therapy that improves motor recovery and decreases muscle atrophy after SCI. The research team will investigate specific inflammatory pathways that link spinal cord injury-mediated macrophage activation and neuromuscular dysfunction. They hypothesize that PDE10A inhibition will improve motor function and reduce muscle atrophy after SCI by decreasing local tissue damage and inflammasome activation.

Progress towards specific aims: To define the mechanistic role of PDE10A-mediated inflammasome activation in macrophages and microglia, the research team made significant progress to show that PDE10A regulates NLRP3 inflammasome assembly and activation. Specifically, they compared two (2) PDE10A inhibitors, TP-10, and MP-10, for their ability to block nigericin or ATP-induced pyroptosis, ASC speck formation, caspase-1 activation, GSDMD cleavage, and IL-1β secretion in lipopolysaccharide (LPS) primed macrophages.

Future Directions: The research team will determine the effects of the PDE10A inhibitors, TP-10, and MP-10, to decrease inflammation and improve functional recovery after in vivo injury. Mechanistically, they will determine the role of the PDE10A-PKA (protein kinase A) pathway on NLRP3 inflammasome assembly. NLRP3, AIM2, and NLRC4 inflammasomes respond to different ligands or activators, but all engage with the adaptor protein ASC and activate protein caspase-1 to cleave pro-IL-1β. To study the specificity of PDE10A for the NLRP3 inflammasome, they will test the effect of TP-10 and MP-10 on the AIM2 and NLRC4 inflammasome. AIM2 will be activated by cytosolic double-stranded DNA (dsDNA). NLRC4 will be activated by cytosolic flagellin.

Impact: These studies will contribute the foundational knowledge needed to develop a new pharmacological treatment that reduces inflammation in response to SCI, and thereby may improve recovery and enhance quality of life.

Publications: Hsu, C.G., Fazal, F., Rahman, A., Berk, B.C., & Yan, C. (2021). Phosphodiesterase 10A Is a Key Mediator of Lung Inflammation. *Journal of Immunology*, 206 (12), 3010-3020.

Institutional Support (Round 7)
Contract Term 07/01/2023-06/30/2028

Progress Reporting Period
07/01/2023-12/31/2023

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

1. **Winifred Burke Medical Research Institute**
   Edmund Hollis, Ph.D.
   $300,000
   BNI Structural and Functional Imaging Core Support

   Introduction/background: Recovery of hand and arm function is the highest priority for tetraplegic individuals living with chronic SCI as it is critical for decreasing long-term care costs and increasing quality of life. The long-term goal is to treat chronic SCI through

circuit-based approaches shaped through an iterative process of bidirectional translational research. The overall objective of this proposal is to establish an electrical stimulation (ES)-modified nerve transfer strategy in mice to restore function after chronic cervical SCI. The central hypothesis is that optimized ES activation of sensory and motor axons critical for movement recovery will improve functional outcomes after nerve transfer for chronic SCI. The rationale for the proposed studies is that a determination of the dose and duration of ES that enhances regeneration after nerve transfer will be directly translatable and will substantially impact current clinical care. The central hypothesis will be tested by pursuing two specific aims: 1) Determine the minimum therapeutically effective dose and duration of ES required to enhance regeneration of sensory and motor neurons; and 2) Evaluate the therapeutic potential of ES to enhance nerve transfer in chronic SCI. The research proposed in this application is innovative, because it addresses a key limitation of a state-of-the-art clinical intervention for ameliorating hand and arm paralysis in individuals with chronic SCI. The proposed research is significant because it is expected to provide a clinically relevant approach to improving surgical outcomes by enhancing novel circuit formation to bypass chronic SCI. These findings will lay the groundwork for optimization of this state-of-the-art intervention for treating chronic SCI.

2. The Research Foundation for SUNY – Stony Brook
Irene Solomon, Ph.D.
$300,000
Neuroprotective Strategies to Minimize SCI Tissue Damage and Improve Bladder and Respiratory Function

Introduction/Background: Spinal cord injury (SCI) directly damages axonal connections between the spinal cord and brain resulting in a reduction or loss of motor, sensory, and autonomic function below the level of the injury. The initial trauma to the spinal cord also initiates a secondary cascade of pathological processes that leads to further injury and tissue loss, and inflammation is suggested to be one of the key mediators in the progression of the secondary injury cascade. Thus, there is a need to develop, implement, and optimize therapies focused on reducing the extent of SCI-induced inflammation and tissue damage/loss to preserve and maximize spared neural substrate and enhance functional recovery. To this end, administration of the antibiotic minocycline (MIN) and the peroxisome proliferator-activated receptor gamma agonist pioglitazone (PIO), which are commonly used FDA-approved clinical agents, have been shown to exert anti-inflammatory and neuroprotective actions in central nervous system (CNS) injury/disease. In SCI, preliminary rodent studies have shown that acute treatment with MIN or PIO decreases multiple processes mediating tissue loss and development of secondary injury, resulting in reduced lesion size and improved hindlimb motor function. While these neuroprotective pharmacotherapies have high potential for clinical use in SCI, the efficacy of these agents on SCIinduced lower urinary tract (LUT) and respiratory dysfunction are unknown.
This IDEA grant application proposes an exploratory/developmental project to test the hypothesis that anti-inflammatory neuroprotective pharmacotherapy using treatment with MIN (SA1) and PIO (SA2) individually and in combination (MIN/PIO; SA3) will significantly reduce neural tissue damage/loss and promote improved spontaneous recovery of bladder (LUT) and respiratory function following acute moderate contusion SCI. The proposed project will also assess the time window for initiating treatment using both immediate (within 15 min post SCI) and delayed (at 24-hr post SCI) treatment to maximize therapeutic efficacy and produce sustained improvements in LUT and

respiratory function. To assess the anti-inflammatory and neuroprotective effects of treatment, anatomical/histological and biochemical (high-throughput Luminex bead-based multiplex immunoassays; immunoblot) assessment of SCI tissue samples at various time points following SCI will be used; these analyses will also provide preliminary insight into potential targets for future mechanistic studies. To assess the effects of treatment on functional improvements, serial measurements of LUT (e.g., transurethral cystometry, metabolic chamber) and respiratory (e.g., plethysmography) function will be obtained before and at various time points up to 4-weeks post SCI. Successful completion of this project will provide an effective noninvasive pharmacology-based neuroprotective intervention using currently available FDA-approved agents to improve bladder control, respiratory function, and quality of life in individuals with SCI.

3. **The Research Foundation for SUNY – Downstate Health Sciences University**
Salvador Dura-Bernal, Ph.D.
$300,000
Restoring Motor Function After SCI Using Multiscale Modeling to Decode Neural Latent Dynamics from Motor Cortex EEG

Introduction/Background: We are developing a novel software tool, called NetPyNE, that enables users to consolidate complex experimental data from different scales into a unified computational model. Users are then be able to simulate and analyze this model to better understand brain structure, dynamics and function in a unique framework that combines: 1. programmatic or GUI-driven model building using flexible, rule-based, high-level standardized specifications; 2. separation of model parameters from underlying technical implementations, preventing coding errors and making models easier to read, modify, share and reuse; 3. support for multiple scales from molecule to cell to network; 4. support for complex subcellular mechanisms, dendritic connectivity and stimulation patterns; 5. efficient parallel simulation both on stand-alone computers and supercomputers; 6. automated data analysis and visualization (e.g., connectivity, neural activity, information theoretic analysis); 7. importing and exporting to/from multiple standardized formats; 8. automated parameter tuning (molecule to network level) using grid search and evolutionary algorithms. NetPyNE's potential to benefit the research community is evidenced by several peer-reviewed publications and by the steady growth of users and advocates. Over 50 researchers and students in our lab and collaborators' labs have used a prototype of the tool for education or to investigate a variety of brain regions and phenomena. There is an active online community who collaboratively contribute to the project, post questions and request features via the GitHub platform, a mailing list and two Q&A forums. The Organization for Computational Neuroscience included a 2-page feature article on NetPyNE in their 2019 Winter Newsletter. NetPyNE is also being integrated with other resources in the neuroscience community: Human Neocortical Neurosolver, Open-Source Brain, Neuroscience Gateway, and the NeuroML and SONATA international standardized network formats. Our proposal is aimed at transforming NetPyNE into a solid and well-tested tool with a fully featured GUI, and widely disseminating the tool among the scientific community. The rapid growth of the tool means many features have been added at a fast pace, with limited resources and time. We will now ensure all these features are properly evaluated for reliability, robustness, and scalability, well documented and incorporated into the GUI. The GUI will also be extended to provide online web-based access and support visualization of larger models. We will also develop interactive online tutorials to clearly explain and demonstrate the ample and diverse functionality included in our package. Through a yearly multi-day course and tutorials/workshops at neuroscience conferences we will

engage and train students, experimental and computational neuroscientists, and clinicians in using NetPyNE for multiscale neural modeling.

Multiscale modeling complements experimentation by combining and making interpretable previously incommensurable datasets. Simulations and analyses developed with NetPyNE provide a way to better understand interactions across the brain scales, including molecular concentrations, cell biophysics, electrophysiology, neural dynamics, population oscillations, EEG/MEG signals, and information flow.

4. **Bronx Veterans Medical Research Foundation**
   Christopher Cardozo, Ph.D.
   $300,000
   Capacity Building at the Spinal Cord Damage Research Center

   Introduction/Background: The objective of the proposed research is to understand whether physical activity is necessary for the enhanced functional recovery observed in mice with a spinal cord injury (SCI) that are treated with new orally active drug candidate, boldine. The mice have a spinal cord injury that is analogous to that experienced by patients who sustain an SCI due to trauma, such as that resulting from a motor vehicle accident, the most common cause of SCI. Boldine is thought the be the major active ingredient of a nutritional supplement made from the Boldo tree, a tree grows in Chile. Boldo is used to prepare teas taken as an herbal remedy for a variety of disorders. Recent studies have demonstrated that one molecular effect of boldine is to plug small holes in cell membranes through which excitatory molecules such as glutamate leak from the cell causing toxicity to nearby nerve cells. The holes are formed by proteins called connexins, and are increased in number on non-neural cells called astrocytes following SCI. In preliminary studies, boldine administered orally to mice increased function of the back legs of mice with spinal cord contusion when evaluated using either of two different tests. These exciting findings stimulated the current proposal, which as noted above is focused on whether physical activity is necessary for these benefits of boldine to occur.

   This is an important question for several reasons. First, it is well established that increasing physical activity through physical therapy can increase function after SCI. Second, there are a few studies showing that physical activity improves functional gains afforded by cell transplant therapies. Third, the current animal models of SCI allow free movement around the cage which is thought to provide a kind of self-rehabilitation through passive movement of the limbs that patients with SCI who cannot walk do not experience. Thus, a comprehensive approach to understanding the impact of physical activity on functional outcomes with or without treatments is needed. The proposed research will set a paradigm for such studies of the intersection of physical activity and drug or cell transplant therapies. In addition, it will establish the role of physical activity.

5. **Icahn School of Medicine at Mount Sinai**
   Hongyan (Jenny) Zou, Ph.D.
   $300,000
   Study Molecular Mechanism of Axon Regeneration After SCI

   Introduction/Background: Adult neurons of the mammalian central nervous system have limited capacity to regenerate axons after spinal cord injury (SCI). In this exploratory proposal, we will study a novel transcriptional regulator Ahr in mediating axon

regeneration after SCI. We hypothesize that Ahr, a known molecular sensor of environmental signals, functions to maintain neural homeostasis at the expense of axon regeneration, and that inhibition of Ahr may present an opportunity to lift this restriction, thereby enhancing functional recovery after SCI. In Aim1, we will examine the impact of manipulating Ahr activity on neurite outgrowth in neuronal cultures. In Aim 2, we will focus on in vivo mouse SCI models to examine the efficacy of attenuating Ahr activity on axon regeneration and functional recovery. In summary, our exploratory proposal will unveil the function of Ahr in regulating axon regeneration potential, thus promises to advance fundamental understanding of transcriptional regulation of regenerative gene programs. Our study also has high translational potential given that an expanding list of small molecular pharmacological drugs are available to modulate Ahr activity, making it a well-suited target for therapeutic interventions aimed at improving functional outcome after SCI.

6. **Regenerative Research Foundation**
   Caitlin Hill, Ph.D.
   $300,000
   Enhancement of Preclinical SCI Infrastructure

   Introduction/background: The development of therapeutic interventions that protect tissue and preserve function following spinal cord injury (SCI), and which can be effective when administered within the first few days as opposed to hours, is badly needed to reduce disability, and maximize function following SCI.

   In a variety of models of neurotrauma and neurological diseases, small molecular inhibitors of exportin 1 (XPO1/CRM1) have demonstrated efficacy at protecting CNS tissue. Karyopharm Therapeutics has developed Selective Inhibitors of Nuclear Export (SINETM), which are potent, orally bioavailable, well-tolerated, centrally active and blood brain barrier penetrant inhibitors of XPO1. Several are in different phases of clinical development. Verdi Nexor (KPT-335), the focus of this proposal, has already undergone rigorous GLP toxicity and pharmacokinetic (PK) evaluation in rats and dog, and has proven to be safe in healthy human volunteers in a Phase 1 clinical trial. In traumatic brain injury (TBI) models, XPO1 inhibition is effective even when administration is delayed for 72 h, and in rat thoracic SCI, it substantially enhances hindlimb recovery and walking (>3 point improvement on the BBB). This supports investigating Verdi Nexor as a therapy for SCI.

7. **University of Rochester**
   Christoph Proschel, Ph.D.
   $300,000
   Promoting Recovery by Inhibiting PDE10A-Mediated Inflammation

   Introduction/background: As part of our efforts to develop new SCI therapies, the University of Rochester has established the SCI Interoperative Network (SCION) at the University of Rochester Medical Center. This network brings together research teams from different departments and across different disciplines, to promote novel avenues in SCI research and to optimize the use of available resources. At present there are five active research groups involved with and different stages of conducting SCI research. SCION greatly reduces the hurdles in engaging in new SCI related studies.

SCION provides expertise in many areas pertaining to SCI and CNS injury and includes equipment and training for rodent spinal cord injury models. Established injury models include the mouse and rat thoracic (T9) contusion SCI, and thoracic and cervical dorso-lateral quadratic hemi section injury. SCION provides a surgical suite, equipped with inhalation anesthesia apparatus, thermal and stereotactic stages, stereotactic injection system, stereomicroscopes (with video monitor for teaching purposes), surgical tools, bead sterilizers, the Infinite Horizons Spinal cord contusion impactor (IH-400) and Ohio State ESCI Device SCI devices and heated recovery cages. Post SCI, SCION also provides support in conducting functional and sensory assays of injured animals. This includes motor-function analysis using video-assisted Catwalk gait system, Gridwalk motor test, Montoya forepaw motility test, Hargraves thermal hyperalgesia testing, and von Frey mechanosensory sensitivity testing. Histological analysis is supported with spinning disc confocal microscope equipped Stereo Investigator and Neurolucida system.

8. **Research Foundation of CUNY – Staten Island**
   Maria Knikou, Ph.D.
   $300,000
   Physiological Properties of Trans Spinal Evoked Potentials in SCI

   Introduction/Background: Spinal reflex characteristics have been attributed to trans spinal evoked potentials (TEPs) following non-invasive trans spinal stimulation in both healthy subjects and people with spinal cord injury (SCI). Further, trans spinal stimulation is currently used in several clinical trials for neuromodulation and neuro-recovery after SCI. The physiological properties of TEPs are not well understood hindering the development of targeted treatments with trans spinal stimulation. The objective of this project is to delineate the physiological properties of trans spinal evoked potentials (TEPs) in people with SCI. We will compare the latency, amplitude, and shape of TEPs in healthy subjects and people with SCI, recruitment input-output curves, and types of motor units engaged in TEPs at rest and during robotic assisted stepping.

9. **The Feinstein Institute for Medical Research**
   Ona Bloom, Ph.D.
   $300,000
   Biomarkers of Immune Dysfunction and Vaccine Responsiveness in People with Chronic Traumatic SCI

   Introduction/Background: Infections are the leading cause of death and re-hospitalization for persons with chronic SCI1,2. Also, most persons with chronic SCI have elevated systemic inflammation, which may impede rehabilitation and promotes many common medical consequences of SCI, e.g., neuropathic pain, cardiovascular disease and stroke3,4. We do not understand the biological mechanisms underlying heightened infection risk or increased inflammation in chronic SCI. This gap in knowledge limits strategies to promote functional abilities, health, survival, and quality of life, and hampers clinical trials, for persons with chronic SCI. To bridge this gap in knowledge, here we propose to use single cell transcriptomic profiling at baseline and in response to vaccination to influenza (flu) and secondarily, to the SARS-CoV-2 virus which causes COVID-19. We will determine relationships of systemic inflammation and vaccine responses (early/innate and late/adaptive immunity), to injury severity.

10. **Rensselaer Polytechnic Institute**

Ryan Gilbert, Ph.D.
$300,000
Polymerized Estrogen Microfibers in Injectable Hydrogels for Astrocyte-Mediated Neurite Guidance and Protection

Introduction/Background: Contusive injuries to the central nervous system provoke acute trauma, inflammation, and swelling, followed by a complex and chronic secondary injury cascade which ultimately prevents full functional recovery. The major female sex hormone 17β-estradiol (E2) has been shown to promote functional recovery in rodent models but requires repeated systemic administration. The team proposes to develop novel implantable biomaterials composed of polymerized pro-drugs of 17β-estradiol (E2), formulated as oriented electro spun microfibers embedded in a matrix of injectable hydrogel. These materials degrade slowly by hydrolysis to release E2 locally. The fibers are made from a linear copolymer of pro-17β-estradiol and a flexible chain linker unit. The hydrogel is formed from 4-arm star polyethylene glycol with terminal units of hydrophobic E2, which forms transient non-covalent crosslinks with poly(β-cyclodextrin) in aqueous solution. Chemically, these polymerized estrogen scaffolds slowly degrade by hydrolysis to release low (nanomolar) doses of E2 locally at the site of the scaffold, sustained for exceptionally long periods of time (months to years), and with the ability to be applied in a minimally invasive manner. The oriented microfibers are proposed to mimic the approximate mechanical properties of fibrillar proteins and will promote mechanical contact guidance cues for controlling the morphology, phenotype, and protein expression in astrocytes and neurons in vitro. The injectable hydrogel matrix surrounding the fibers is intended to mechanically match the stiffness of very soft tissue in the central nervous system. The central goal of this research project is to relate the material properties to the cell response. The team will synthesize a library of polymerized E2 variants with systematically tuned chemical structures. The hydrophobicity and chain flexibility will be varied, which in turn will influence mechanical properties, surface topology and the rate and mechanism of degradation and drug release. These materials will then be incubated with astrocytes and neurons to assess the impact of their properties on the cell behavior observed. The goal is to understand how to orchestrate cell response to biomaterials that can promote regenerative phenotypes and possibly improve the likelihood of functional recovery.

11. The Trustees of Columbia University in the City of New York
Sunil Agrawal, Ph.D.
$300,000
Recovery of the Movement After SCI Using Robotics and Spinal Cord Stimulation

Introduction/Background: The objective of this project is to assess the effects of dynamic assistance provided by WRAPS on wheelchair users with severe SCI during i) static/dynamic postural control, ii) reaching activities; and iii) control of under-seat pressure.

Specific Aim 1: To quantitatively compare the range of motion of the upper body and arms during reaching tasks while seated in a wheelchair, using active assistance with WRAPS versus passive support to maintain trunk balance.

Specific Aim 2: To evaluate the effectiveness of pressure relief maneuvers of the upper body made by WRAPS when compared to self-motions performed by users.

Our hypotheses for the two aims are as follows: H1 –The comfortable range of motion during reaching tasks can be significantly improved by active assistance with WRAPS. H2 – Pressure relief maneuvers performed with WRAPS will be at least as effective as self-maneuvers by subjects.

12. Research Foundation of CUNY obo City College of New York
Ashiwel Undieh, Ph.D.
$300,000
Strengthening SCI Research at the CUNY School of Medicine

Introduction/Background: Promoting significant motor function after SCI will depend on combined structural and physiological plasticity to reconnect the brain with the spinal cord below the injury. Promoting long-distance axonal outgrowth beyond the injury currently is not possible. However, since most SCIs are incomplete, spared axons caudal to the injury are an important target for therapy to repair and restore function. The problem is how to make spared axon sprouting sufficiently robust to transmit signals to spinal targets denervated by the injury.

In this proposal we focus on the corticospinal tract (CST), which is essential for skilled voluntary movements. We will leverage LTP in motor cortex to help promote CST sprouting in the spinal cord, through upregulation of mTOR and downregulation of PTEN signaling; these are key components of the CST axon growth state. We use a neuromodulation protocol termed intermittent theta burst stimulation (iTBS), which produces LTP in the cortex of animals and humans. We have shown that iTBS additionally promotes CST axon sprouting. In this proposal, we hypothesize a linkage between the occurrence of persistent, or late LTP and the establishment of the CST axon growth state in CST neurons. By augmenting late LTP we hope to promote the CST axon growth state and enhance CST sprouting. This is a novel target to amplify sprouting. Further, we aim to show that a CST growth state can be achieved not only using electrical brain stimulation but also by repetitive TMS.

We will examine the question of the role of persistent LTP produced by epidural motor cortex electrical iTBS and growth. In Aim 1, we will use a chemogenetic approach, DREADDs, to excite cortical neurons and augment LTP produced by iTBS. We hypothesize that this will elevate the CST axon growth state and, in turn, enhance further CST axon sprouting in the spinal cord. To understand mechanisms, we will chemo genetically inhibit cortical neurons to reduce LTP and the CST axon growth state and, in turn, lessen or eliminate CST axon sprouting. In Aim 2, we will study animals with a C4 midline contusion. We will use chemogenetic excitation to boost the neuromodulation-induced growth state, which seems to be a muted after injury, to augment CST sprouting. We will also determine if promoting persistent LTP leads to improved motor function in injured animals. In Aim 3, we will determine if iTBS produced by a TMS device can activate the CST axon growth state. We will use a new state-of-the-art TMS coil together with computational modeling (FEM) to inform the use of TMS to activate CST axon growth and determine if outcomes are comparable to that produced by electrical stimulation.

Our results will both inform the mechanism of activity-based neuromodulation for promoting CST outgrowth and will help guide development and implementation of neuromodulation protocols in humans.

13. Albany Research Institute, Inc.

Jonathan R. Wolpaw, M.D., Ph.D.
$300,000
Targeting and Enabling Beneficial Plasticity to Produce Recovery After SCI

Introduction/Background: Spinal cord injury (SCI) impairs voluntary movement because it damages the descending and ascending connections between the brain and the spinal cord. Most rehabilitation research aims to restore the descending connections through which the brain controls the muscles; less attention has been given to restoring the ascending connections that bring movement-related sensory input to the brain. Nevertheless, many studies show that sensory input is essential for effective movement. Loss of sensory input impairs voluntary movement and limits motor rehabilitation. Sensory loss is correlated with a smaller or delayed somatosensory evoked potential (SEP). This project aims to develop and test a novel SEP-based noninvasive therapy for restoring effective sensory connections in people with iSCI. Our expectation is that this new therapy can complement existing therapies and enhance lasting functional recovery beyond that now possible.

Our lab and several others have recently developed and validated the new rehabilitation strategy of Targeted Neuroplasticity (TNP) with operant conditioning of evoked responses. TNP uses a noninvasive protocol to target beneficial change to a CNS site that is crucial for an important behavior, such as locomotion or reach-and-grasp. The resulting targeted plasticity directly benefits performance and, in addition, facilitates effective practice that leads to widespread beneficial change that improves the entire behavior. Moreover, the functional improvement persists for months after conditioning. This has been extensively studied for spinal reflex conditioning where locomotion improvements were observed in people with iSCI. Here we propose to target the cortical SEPs, that are known to be delayed and reduced in amplitude after iSCI and are related to functional recovery. Based on the spinal conditioning research and the vast literature on somatosensory peripheral nerve stimulation, we hypothesize that: 1) SEP conditioning will be successful in most people with iSCI; 2) it will improve sensory and motor function; and 3) these improvements with persist.

We will develop and test this protocol in 10 healthy people, using our existing hardware and software platform called Evoked Potential Operant Conditioning System (EPOCS). EPOCS was developed by our labs over many years and has been applied successfully in conditioning of H-reflexes and motor evoked potentials. It supports real-time closed-loop feedback of a CNS evoked response and assists the patient to gradually change the size of evoked response over multiple sessions, with the help of visual feedback and reward. We will apply it in 24 people with iSCI (12 of 24 will form a Control group) over 10 weeks (6 baseline, 24 conditioning sessions, 2 follow-ups, 3/week). SEP will be recorded with scalp electroencephalography (EEG) to median nerve stimulation at the wrist. The functional and physiological impact will be assessed at pre, post and follow-up 3 & 6 mo., by standard hand function tests (by a blinded Physical Therapist) and physiological assessments with transcranial magnetic stimulation and robot-based task-related EEG (to measure cortico-cortical connectivity, cortico-muscular coherence, event related desynchronization).

If successful, the significance would be an important noninvasive therapeutic advancement towards restoring impaired sensation and enhancing motor recovery in people with iSCI. This new method could complement other therapeutic methods and

augment recovery. Because the SEP conditioning can be targeted to a specific afferent pathway (e.g., proprioceptive, nociceptive), and direction (up-condition proprioceptive sensation; down-condition abnormal nociceptive responses) it could be personalized for each person's particular needs. Potential next steps are to test it for lower limb function in iSCI, and for other disorders with movement impairment. The longer-term goal is to develop a wearable device for sensory conditioning that can be used independently, along with motor rehabilitation, for larger functional gains and improved quality-of-life.

Institutional Support (Round 6)
Contract Term 03/01/2017-02/28/2022

Progress Reporting Period
09/01/2021-02/28/2022

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

1. **Albany Research Institute, Inc. – Albany Stratton VA Medical Center**
   Jonathan R. Wolpaw, M.D., Ph.D.
   $242,500

   Funding supported staff who direct aspects of SCI work; their work will enable new applications focused on developing new therapeutic methods that enhance recovery for people with SCI.

2. **Albert Einstein College of Medicine (AECOM)**
   David J. Sharp
   $242,500

   No further progress has been submitted for the final period at the time the report was prepared. In 2021 it was previously reported, research supported by this funding is aimed at elucidating the therapeutic potential of targeting the novel microtubule regulatory protein FL2 to promote axonal regeneration after SCI. The data generated with this funding will further the research team's understanding of how the microtubule cytoskeleton regulates axonal growth, and may potentially provide the groundwork for a novel therapeutic target for promoting functional recovery after SCI. Their data has been used to apply for several SCI and nerve regeneration related grants. A manuscript is under review.

3. **Bronx Veterans Medical Research Foundation – James J. Peters VA Medical Center**
   William A. Bauman, M.D.
   $242,500

   Funding supported personnel on current proof-of-concept studies such as determining the precision of dual energy x-ray absorptiometry scans and bioimpedance spectroscopy in SCI and able-bodied individuals. The research team feels strongly that the preliminary work will lead to several grant applications. Genetic analyses will serve as one of the primary study outcomes for which a future clinical trial may be designed.

   Publications: Cirnigliaro, C.M., Myslinski, M.J., Parrott, J.S., Cross, G.T., Gilhooley, S., La Fountaine, M.F.,…& Bauman, W.A. (2022). Generation of a Reference Dataset to Permit the Calculation of T-scores at the Distal Femur and Proximal Tibia in Persons with Spinal Cord Injury. Journal of Clinical Densitometry, 25(3):308-318.

4. **Columbia University**
   Sunil k. Agrawal, Ph. D.
   $242,500

Funding supported Sunil Agrawal, Ph.D. in the assembly, testing, and research of the two pelvic support systems to advance current rehabilitation methods and develop innovative solutions to reduce risk of falls for SCI patients.

Right now, the engineering feasibility of the two systems are being verified. In the coming years, the systems will be extended for pilot studies with SCI participants.

Publications: Chang, B.C., and Agrawal, S.K. (2021). Stability During Stairmill Ascent with Upward and Downward Applied Forces on the Pelvis. IEEE Transactions on Neural Systems and Rehabilitation Engineering, 29, 1504-1512.

Chang, B.C., and Agrawal, S.K., (2022). Change in Muscle Synergies During Stairmill Ascent with External Forces on the Pelvis. IEEE Robotics and Automation Letters, 7(3), 7247-7254.

5. **Cornell University**
   Chris B. Schaffer
   $242,500

   This funding supplied equipment and partial funding for animal housing and supplies needed for SCI experiments with mice, specifically for imaging aimed at understanding the normal function of spinal cord circuits in coordinating limb motion. The research team is preparing a manuscript on the capabilities and limits of the three-photon imaging in the mouse spinal cord, with demonstration experiments in spinal cord blood flow and spinal cord stroke.

   The advanced imaging and image processing capabilities enabled by this funding were instrumental in the award by the National Science Foundation to the principal investigator, Dr. Chris Schaffer, and his team. A collaborative award funded to the Buke Institute (National Institutes of Health, Research Project Grant, R01) also included using the three-photon imaging in the spinal cord.

6. **Feinstein Institute for Medical Research**
   Ona Bloom
   $242,500

   This grant provided partial salary support and lab supplies for three ongoing projects that share the goal of improving the understanding of how to best promote neurological recovery and wellness in people with SCI.

   Publications: Katz, H., Arcese, A.A., Bloom, O., & Morgan, J.R. (2022). Activating transcription factor 3 (ATF3) is a highly conserved pro-regenerative transcription factor in the vertebrate nervous system, *Frontiers in Cell, and Developmental Biology*, 10, 1-11.

Bloom, O., Tracey, K.J., & Pavlov, V.A. (2022. Exploring the vagus nerve and the inflammatory reflex for therapeutic benefit in chronic spinal cord injury. *Current Opinion in Neurology*, 35, 249-257.

Bloom, O., & Guest, J. Editorial update on current topics in traumatic spinal cord injury, *Current Opinion in Neurology*, 34 (6), 781-782.

Presentations: Bloom, O. *Biomarkers of Spontaneous Recovery from Traumatic Spinal Cord Injury*, American Spinal Injury Association, Annual Meeting, Virtual 2021.

7. Health Research, Incorporated
Bruce J. Herron
$242,500

Funding supported ongoing work to develop molecular methods to determine how transcriptional changes in spinal cord activity are correlated in rats with SCI responses to the various forms of therapy designed to recover motor function. Data collected is expected to be used to support future applications for funding.

Presentations: Herron, B.J., Wang Y., Chen, Y., Chen, X.Y., Vato, A., Carp, J.S., & Wolpaw, J.R. *Electrocortical stimulation (ECS) of rat sensorimotor cortex (SMC) may regulate glutamate ionotropic AMPA receptors and their associated mRNA in spinal cord motoneurons*. Society for Neuroscience Annual Virtual Meeting 2021.

Wang, Y., Herron, B.J., Chen, Y., Vato, A., Carp, J.S., & Wolpaw, J.R. *Electrocortical stimulation of rat sensorimotor cortex increases VgluT2-labeled terminals on spinal motoneurons and changes gene expression of Chx10-positive spinal interneurons.* 8th Annual BRAIN Initiative Virtual Meeting 2022.

8. Icahn School of Medicine at Mount Sinai
Hongyan (Jenny) Zou, M.D., Ph.D.
$242,500

This funding supported Principal Investigator, Hongyan Zou, M.D., Ph.D. and Co-Principal Investigator, Roland Friedel, Ph.D., who directed their laboratories to generate data on novel function of Plexin-B2 signaling in mediating innate immune response after SCI and after peripheral nerve injury. They have received a NIH R01 grant to extend their findings on how Plexin-B signaling is involved in organizing the glial nets surround amyloid plaques in other CNS diseases.

Publications: Li, Y., Kang, S., Halawani, D., Wang, Y., Junqueira Alves, C., Ramakrishnan, A.,…& Zou, H. (2022). Macrophages facilitate peripheral nerve regeneration by organizing regeneration tracks through Plexin-B2. *Genes Dev*, 36(3-4):133-148.

Wahane, S., Halawani, D., Zhou, X., & Zou, H. (2019). Epigenetic Regulation of Axon Regeneration and Glial Activation in Injury Responses. *Front Genet*, 10:640.

Presentation: Zou, H. *Microglia/Macrophages Orchestrate Regenerative Track & Glial Organization after Axonal Injury.* Gordon Research Conference on Central Nervous System Injury and Repair, Oxnard, California, 2022.

9. New York University
Esteban O. Mazzoni
$242,500

Funding supported staff and lab supplies for the development of a robust human motor neuron differentiation protocol producing high-quality cranial motor neurons (CMNs) and spinal motor neurons (SMNs). They have established a stem cell-based system to investigate the mechanisms that protect human CMNs from neurodegeneration. These two motor neurons have different splicing responses to stress. It is well described that SMNs develop several splicing defects when stressed or in amyotrophic lateral sclerosis (ALS), but it is not described how CMNs develop splicing defects in response to stress. Their recent results suggest that CMNs have fewer splicing defects under stress. Moreover, SMNs' specific splicing defects are in genes associated with protein degradation and splicing. Thus, the ALS-sensitive SMNs seem to enter a futile degeneration spiral, where proteotoxic induces splicing defects that cause more proteotoxic stress.

Results obtained from this funding supported new grant applications: one is pending, and one is funded by the Chan Zuckerberg Initiative Neurodegeneration Challenge Network (NDCN) to produce human motor neurons to analyze the effect of C9orf72 (a gene providing instructions for making a protein that is found in various tissues) mutations.

Publications: An, D., Fujiki, R., Iannitelli, D.E., Smerdon, J.W., Maity, S., Rose, M.F., &…Mazzoni, E.O. (2019). Stem cell-derived cranial and spinal motor neurons reveal proteostatic differences between ALS resistant and sensitive motor neurons, *eLife* 8: e44423.

(Preprint) Iannitelli, D.E., Tan, A., Nguyen, E., Babu, A., Elorza, S.D., Joseph, T.,…& Mazzoni, E.O. (2022). ALS sensitive spinal motor neurons enter a degenerative downward spiral of impaired splicing and proteostasis. *bioRxiv,* 485939.

10. Regenerative Research Foundation
Thomas R. Kiehl
$242,500

Funding was used to support Liz Fisher, Ph.D., for manuscript preparation, manual annotation of data and cell types, sample tracking, preparation and staining, and animal care; Nathan Boles, Ph.D., for advisement on analysis and cell markers; and Thomas

Kiel, Ph.D., for project management, data analysis and equipment management/maintenance and figure preparation.

Creating a strong foundation for single-cell transcriptome analysis within their organization has impacted nearly every research program at their institution. Their data regarding the long-term activation of B cells within the injury milieu will serve as preliminary data that they can use to pursue further funding and they also received a federal grant.

A publication describing their findings is currently under review and a pre-release of their publication is below. The data will be made on the Gene Expression Omnibus (GEO) and their analysis code will be released via GitHub. References to their products will be collected and presented on their website alongside other datasets from their organization, http://neuralsci.org/computing.

Publications: (Preprint) Fisher, E.S., Amarante, M., Lowry, N., Lotz, S., Farjood, F., Temple, S. &…Kiehl, T.R. (2022). Single Cell Profiling of CD45+ Spinal Cord Cells Reveals Microglial and B Cell Heterogeneity and Crosstalk Following Spinal Cord Injury *bioRxiv*, 486287.

11. Rensselaer Polytechnic Institute
Ryan J. Gilbert, Ph.D.
$242,500

This funding supported student stipends and partially supported salary of research staff. The funding was used to support several other projects that were funded by the National Institutes of Health (Grant NS092754), Paralyzed Veterans of America (Grant 3171), and the Craig Neilsen Foundation (Grant 468116). Funds from the institutional support grant were used to support these projects (pay for additional supplies, cover graduate student stipend support, partially pay for post-doc time) for the development of biomaterials and drug delivery vehicles for SCI applications.

Publications: Funnell, J.L., Ziemba, A.M., Nowak, J.F., Awada, H., Prokopiou, N., Samuel, J.,…& Gilbert, R.J. (2021). Assessing the combination of magnetic field stimulation, iron oxide nanoparticles, and aligned electro spun fibers for promoting neurite outgrowth from dorsal root ganglia in vitro. *Acta Biomaterialia*, 131: 302-313.

Nelson, D.W. & Gilbert, R.J. (2021). Extracellular matrix-mimetic hydrogels for treating neural tissue injury: a focus on fibrin, hyaluronic acid, and elastin-like polypeptide hydrogels. *Advanced Healthcare Materials,* 10: 2101329.

Nelson, D.W., Puhl, D.L., Funnell, J.L., Kruger, U., & Gilbert, R.J. (2022). Multivariate analysis reveals topography dependent relationships amongst neurite morphological features from dorsal root ganglia neurons. *Journal of Neural Engineering,* 19: 036026.

Puhl, D.L., Mohanraj, D., Nelson, D.W., & Gilbert, R.J. (2022). Designing electro spun fiber platforms for efficient delivery of genetic material and genome editing tools. *Advanced Drug Delivery Reviews,* 114161.

12. Research Corporation of Long Island, Inc. – Northport VA Medical Center
Victor L. Arvanian
$242,500

The research team has several new insights regarding the possible processes and mechanisms of PSEMS (pulse at 20 Hz frequency for 5 sec with 25 sec break between pulses, total 40 trains for 20 minutes) They hypothesize that Buprenorphine and PSEMS might share common sites of action and suggest that PSEMS might carry potential to recover, at least partially, some deficits, including pain, after SCI. Preliminary results of their on-going pilot study indicate that PSEMS may induce reduction of chronic low back pain (CLBP) in humans and thus can serve as an effective, non-invasive treatment approach for chronic low back pain.

During reporting period, they completed two major goals. They used a chronic contusion SCI model and established parameters of the SEMS that would reverse changes in H-reflex parameters occurred during chronic stage of SCI in rats. They also applied SEMS in veterans with CLBP, using SEMS parameters established in SCI rat model, in attempt to reduce LBP and improve quality of life of the veterans.

This research provides a strong foundation for translation results of their animal experiments into humans. Administration of electro-magnetic stimulation (EMS) at spinal levels to stimulate spinal roots is FDA approved. They have begun using EMS in human studies at Northport VA (collaboration with Dr. Fahmy) and Stony Brook University (Collaboration with Dr. Sisto). Some results of their human study have been recently published (Petrosyan et al., 2020; Arvanian et al., 2022).

Presentations: Petrosyan, H., Fahmy, M., Tesfa, A., Arvanian, V.L. *Spinal electromagnetic stimulation to reduce chronic low back pain in humans and corresponding plasticity in spinal cord injured rats,* Federation of European Neuroscience Societies, Virtual Forum 2020.

Publications: Petrosyan, H., Liang, L., Tesfa, A., Sisto, S.A., Fahmy, M., & Arvanian, V.L. (2020). Modulation of H-reflex responses and frequency-dependent depression by repetitive spinal electromagnetic stimulation: from rats to humans and back to chronic spinal cord injured rats. *The European Journal of Neuroscience*, 10, 0-15.

Arvanian, V.L., Liang, L., Tesfa, A., Fahmy, M., & Petrosyan, H.A. (2022). Buprenorphine, a partial opioid agonist, prevents modulation of H-reflex induced by pulsed electromagnetic stimulation in spinal cord injured rats. *Neuroscience Letters*, 777, 136583.

13. Research Foundation for SUNY – Downstate Medical Center
Ashiwel Undieh
$242,500

Support was requested to support the salary of a graduate student, focused on the primary motor cortex (M1) microcircuits modeling. The project elucidates M1 neural coding mechanisms to help build autonomous bidirectional brain-machine interfaces for SCI patients. They completed their objective of better understanding neural coding mechanisms using a computational simulation of M1 neural circuits and submitted a publication with their findings that's currently under review.

Despite several large-scale modeling efforts, the motor cortex (M1) region, which is essential to understand motor disorders and lesions, had not yet been modeled in detail. Their model addresses this knowledge gap and provides multiscale mechanistic explanations of in vivo observations that can help other researchers interpret their own findings. Researchers and clinicians can design experiments to test the model predictions, as well as adapt the model to incorporate new data, and generate novel hypotheses and predictions across a wide range of scales. Overall, their work will enable to better understand and treat SCIs.

Multiple projects have already benefited from the research supported through this funding plus several other grants are in the review process or in preparation.

Publications: Anwar, H., Caby, S., Dura-Bernal, S., D'Onofrio, D., Hasegan, D., Deible M, Grunblatt, S.,…Neymotin, S.A. (2022). Training a spiking neuronal network model of visual-motor cortex to play a virtual racket-ball game using reinforcement learning. *Public Library of Science One,* 17(5): e0265808.

Awile, O., Kumbhar, P., Cornu, N., Dura-Bernal, S., King, J.G., Lupton, O.,…& Schürmann, F. (2022). Modernizing the NEURON Simulator for Sustainability, Portability, and Performance. *Frontiers in Neuroinformatics*, 16:884046.

Kelley, C., Dura-Bernal, S., Neymotin, S.A., Antic, S.D., Carnevale, N.T., Migliore, M,…& Lytton, W.W. (2021). Effects of Ih and TASK-like shunting current on dendritic impedance in layer 5 pyramidal-tract neurons. *Journal of Neurophysiology, 10.1152/jn.00015.2021.*

Romaro, C., Najman, F., Lytton, W.W., Roque, A.C., & Dura-Bernal, S. (2021). NetPyNE implementation and rescaling of the Potjans-Diesmann cortical microcircuit model. *Neural Computation*, 33 (7): 1993–2032.

Sekiguchi, K., Medlock, L., Dura-Bernal, S., Prescott, S.A., & Lytton, W.W. (2021). Multiscale computer model of the spinal dorsal horn reveals changes in network processing associated with chronic pain. *Journal of Neuroscience*, 42 (15) 3133-3149.

(Preprint) Borges, F., Moreira, J., Takarabe, L.M., Lytton, W.W., & Dura-Bernal, S. (2022). Large-scale biophysically detailed model of somatosensory thalamocortical circuits in NetPyNE. *bioRxiv*, 479040.

(Preprint) Dura-Bernal, S., Griffith, E.Y., Barczak, A., O'Connell, M.N., McGinnis, T., Schroeder, C.,…& Neymotin, S.A. (2022). Data-driven multiscale model of macaque auditory thalamocortical circuits reproduces in vivo dynamics. *bioRxiv*, 479036.

(Preprint) Dura-Bernal, S., Neymotin, S.A., Suter, B.A., Dacre, J., Schiemann, J., Duguid, I.,…& Lytton, W.W. (2022). Multiscale model of primary motor cortex circuits reproduces in vivo cell type-specific dynamics associated with behavior. *bioRxiv,* 479040.

14. Research Foundation for SUNY – Stony Brook
Zaghloul Ahmed
$242,500

The supplies purchased can be used by SCI researchers that are generating rodent contusion SCI models and/or examining the efficacy of various therapeutic interventions on tissue-level biomarkers as part of their evaluation. This information could aid in the identification of potential cellular targets in the development of future mechanistic studies and grant applications.

The equipment with this funding has been integrated into the SCI core facilities (SCI surgical core, physiological measurement core, biochemical assays/analysis core, motor behaviors assessment core, histology/imaging core, and SCI intervention core) and are in use by SCI investigators at the University.

To date, pilot data have been produced using the SCI core facilities equipment and these data are included in grant applications. Thus, the equipment purchased is essential for enhancing funding of future SCI research.

15. Research Foundation for SUNY – University at Albany
Ben G. Szaro
$242,500

Funding supported researchers, Drs. Ben Szaro, Morgan Sammons, Jamie Belrose, Sergei Reverdatto, and Aparna Prasad. They predict that the ChIP-seq data, whole genome bisulfite sequencing (WGBS) data, and 5hmC MeDIP-Seq data will become a valuable resource for studying the epigenetics of SCI and other forms of CNS injury. By comparing differences in epigenetic states between situations where CNS axons successfully regenerate against those that do not, they have gained fundamentally new insights into molecular mechanisms underlying the success or failure of regenerative responses to CNS injury in a vertebrate animal model.

The raw sequencing data and the BigWig files derived from these have now been deposited at the National Center for Biotechnology Information (NCBI) in their Gene Expression Omnibus (GEO) database under accession numbers GSE137644 and GSE183357. The large databases generated by this funding are likely to used extensively by the field. They are described in detail in the two publications in *BioMed Central Genomics*, which are listed below. As of the writing of this report, the paper describing the RNA-seq dataset and analysis (Belrose et al., 2020) has already been accessed over 2,000 times and cited five (5) times.

The preliminary data contributed to National Science Foundations and NYSDOH SCIRB awards. Unfortunately, because of the COVID-19 delays, the personnel who were to carry out these studies had to take other jobs. These departures, combined with other

issues stemming from the pandemic, encouraged the PI, Dr. Ben Szaro, to retire in 2022. Nevertheless, an outside collaborator, Dr. Kurt Gibbs (Morehead State University) plans to continue with the work on SCI in Xenopus and will likely use the resources generated by this project to support future work and funding applications.

Publications: Belrose, J.L., Prasad, A., Sammons, M.A., Gibbs, K.M., & Szaro, B.G. (2020). Comparative gene expression profiling between optic nerve and spinal cord injury in Xenopus laevis reveals a core set of genes inherent in successful regeneration of vertebrate central nervous system axons. *BioMed Central Genomics,* 21: 540.

Reverdatto, S., Prasad, A., Belrose, J.L., Zhang, X., Sammons, M.A., Gibbs, K.M., & Szaro, B.G. (2022). Developmental and injury-induced changes in DNA methylation in regenerative vs. non-regenerative regions of the vertebrate central nervous system. *BioMed Central Genomics,* 23:2.

16. Research Foundation of CUNY – Staten Island
Salvador Dura-Bernal
$242,500

Funding provided partial support for two (2) researchers to perform experiments. They completed experiments in animals with SCI (some with neural tracer at the lumbar spinal cord and some at the motor cortex). In these experiments, they used a new stimulation device using implanted hydrogel electrodes to deliver direct current to the injured segments of the spinal cord. Animals were briefly stimulated for 21 days, injected with neural tracers, and then followed for another few weeks. They observed that animals scored significantly better in the Bristol-Myers Squibb scale (walking better) and exhibited more regrowth in the sensory axons of the injured spinal cord. Their findings will be submitted for publication and results will be used to apply for grant applications.

17. Research Foundation of CUNY – The City College of New York
Irene C. Solomon
$242,500

Funding provided support of research supplies and general laboratory supplies, animal procurement and husbandry, and scientific meeting participation for dissemination of research results. Overall, these purchases contributed to the goal of the project, to build capacity for mechanism-based pharmacological approaches to SCI research at the City College of New York (CCNY). Successful mastery of the research team's experimental techniques as well as data generated from experiments would then facilitate additional resources to support a larger program of mechanism-based drug discovery for SCI. Data generated from this project contributed to a manuscript in preparation, two (2) abstracts and to two (2) new grant proposals under review.

Presentations: Kang, W., Tchamna, A.D.S., & Undieh, A.S. (2021): *Neurodegenerative Neurotrophic Effect Mediated by Agents that Promote Cytidine Diphosphate Diacylglycerol Biosynthesis*. Society for Neuroscience, Virtual Meeting 2021.

18. Syracuse University

Katharine E. (Kate) Lewis
$242,500

The materials, resources and data generated through this funding generated essential components and preliminary data for a full proposal that was submitted and funded by the National Science Foundation (NSF) to analyze the created mutants in more detail and establish a fully characterized Gene Regulatory Network for the specification of V0v neurotransmitter properties. The funding helped the research team to establish and maintain essential mutant lines, which are important for future grant applications.

19. University of Rochester
Mark D. Noble
$242,500

Funding provided support to develop the abilities of the University's Spinal Cord Injury Operational Network (SCION) to serve the needs of the SCI research community and helped the princiapl investigators recruit new investigators to the field of SCI research.

SCION provides a central hub that enables high quality SCI research in multple laboratories, without requiring each laboratory to create its own unique resource and equipment base. SCION currently is equipped for traumatic spinal cord injury models (Infinite Horizons spinal cord contusion impactor), behavioral and sensory analysis (Catwalk gait analysis system, Gridwalk motor test, staircase forepaw motility test, Hargraves thermal hyperalgesia testing), electrophysiological analysis (motor evoked potential and somatosensory evoked potential measurements, intra-spinal evoked field potential measurements, in vitro multi-electrode array testing), treadmill-based physical therapy and advanced microscopy using design-based stereology (MicroBrightField Stereo Investigator and Neurolucida systems).

20. Winifred Masterson Burke Medical Research Institute
Rajiv R. Ratan
$242,500

Funding has provided additional preliminary data for revised submissions. The research team held Institutional-level discussion between Burke Neurological Institute and Kessler Rehabilitation Institute about ways to facilitate and grow SCI clinical trials. This relationship has led to further collaborations between Burke researchers and Kessler researchers to facilitate recruitment and completion of an ongoing repetitive transcranial magnetic stimulation (rTMS) feasibility and safety study. Due to COVID-19 delay, the trial is ongoing, and once completed, the results will be presented at an appropriate national meeting and a manuscript will be prepared.

This funding has been used, in part, to develop the infrastructure to support an expanding spinal cord research focus which was instrumental for recruitment. A recent recruit, Dr. Yutaka Yoshida, has been received an SCIRB IDEA and PART award.

Translational Research Projects in SCI (Round 2)
Contract Term 5/1/18-4/30/22, NCE through 4/30/23

Progress Reporting Period
11/1/21-4/30/22

2 Awards, Procurement Total: $2,827,075

1. **Health Research, Inc.**
   Jonathan R. Wolpaw, M.D., Ph.D.
   $1,623,620
   A Spinal Reflex Conditioning System Suitable for Clinical Translation

   Introduction/Background: Current rehabilitation for people with Spinal Cord Injury (SCI) consists mainly of pharmaceutical and physical therapies. Despite these treatments, deficits usually remain and impair basic skills such as walking. Recovery could be enhanced by targeted neuroplasticity therapies that produce long-term beneficial changes in the spinal cord. Among the first of these new therapies are spinal reflex operant conditioning protocols; by modifying abnormal reflex pathways, they thereby improve walking and other skills. At present, these protocols require a complex software/hardware system usable only by highly trained experts. The project goal is to translate this cumbersome laboratory system into a robust simple system suitable for widespread use by clinical therapists.

   Progress Towards Specific Aim: During the second half of Year 4, we have:

   - Further developed and validated the new version of the Evoked Potential Operant Conditioning System (EPOCs) software system:
     - Made progress simplifying the clinician's experience of the selection of stimulation and recording sites testing and using the multielectrode array.
     - Developed an algorithm that, with further testing, should permit objective, repeatable determination of the parameters of soleus H-reflex and M-wave measures, enabling a fully automated analysis of the corresponding recruitment curves.
     - Developed a means to follow small movements in the arm during training to evaluate the impact of positional changes on session-to-session variability and outcomes.
   - Continue to develop and test multi grid electrodes for clinical applications.
   - Begun to design and test the housing for the hardware in clinical environments in accord with FDA guidelines.
   - Created, beta-tested, and modified materials for researchers, clinicians and for their patients. These include:
     - Designed, submitted, and scheduled a Journal of Video Experiments (JoVE) recording that will explain operant conditioning and the EPOCs system.

- An informational brochure.
- A public website listing basic scientific and technical background on theory of operant conditioning (OC).
- A technical manual.
- The design of a six-hour hands-on workshop as an introduction to OC and EPOCS software and hardware.

- Continued to test each part of the new system and the system for reliability, safety, convenience, and ability to function effectively with human subjects. This includes but is not limited to:
  - testing the multielectrode recording array platform to verify that a combination of multichannel stimulation and multielectrode recording in a single platform will better serve clinicians who wish to perform operant conditioning therapy.
  - continuing to develop and validate a novel behavioral task to evaluate changes in myoelectric signals due to operant conditioning.
  - performing *in silico* experiments using a computational model of the spinal cord to theorize off-target effects of operant conditioning.

Impact: The Evoked Potential Operant Conditioning System (EPOCS) suitable for clinical translation, developed during this SCIRB-funded project, will enable, and accelerate the establishment of spinal-reflex operant conditioning (OC) as a unique and important new therapeutic method. The new system supports other conditioning research protocols, for example operant conditioning of H-reflexes of the upper limb. It also presents opportunities for combining OC training with other noninvasive therapeutic approaches that can enhance recovery of function for people with spinal cord injury or other neuromuscular disorders. Finally, these studies have been an important factor in the success of a NIH-funded Small Business Innovation Research (SBIR) proposal entitled, “Spinal Reflex Conditioning System for Enhancing Motor Function Recovery after Incomplete Spinal Cord Injury” (U44 NS114420). This work is now underway as a collaboration between the Medical University of South Carolina, Stratton VAMC, and BioCircuit, Inc. This SBIR includes funding for a clinical trial to begin next year.

2. University of Rochester
Mark Noble; Christoph Proschel, Ph.D.
$1,203,455
Pharmacological Treatment of Acute Spinal Cord Injury

Introduction/Background: Transition of medically relevant discoveries to the clinic is generally based on the assumption that benefits in pre-clinical models are translatable to therapeutic approaches in humans. However, most clinical trials end in failure, suggesting that well-designed translational efforts need to address both promising discoveries and possible reasons for clinical failure. Our SCI research is designed to provide promising new treatments and to identify and overcome factors that might limit success in clinical trials.

Progress Towards Specific Aims: The general focus of our research is treatment with the potassium channel blocker 4-aminopyridine (4AP), starting 18-24 hrs after injury, and

our studies thus far indicate that effects of 4AP are sufficiently robust to jusitify planned progress to clinical trials.

During the past year we have conducted experiments on two questions relevant to the clinical translation of our discoveries. The first of these is an analysis of the effects of age on the response to 4AP treatment of acute traumatic SCI. This is important because most experiments in this field are conducted on rats that are 8-10 weeks old. Such rats are developmentally equivalent to young teenage humans, in terms of spinal cord structure and function. We therefore have conducted contusion injuries on 1 year old rats, which are thought to be developmentally more equivalent to 30-year-old humans. This is a particularly important set of experiments because the few studies conducted on 1 year old rats suggest their response to injury is more severe than seen in younger animals. Secondly, we have combined physical therapy with 4AP treatment to test whether the physical therapy would unexpectedly decrease the benefits of 4AP. This is important to know as one benefit of 4AP treatment is earlier improvement in motor function. In humans, such an outcome would lead to earlier initiation of physical therapy.

Future Directions: We are continuing the analyses of effects of 4AP on the recovery of 1 year old rats, with an expanded number of animals and a longer treatment period.

Impact: The impact of this work is in several areas. The analytical approach we've implemented indicates 4AP treatment is robust enough to be useful across a range of injury variability greater than is embraced in most studies and allows early integration with physical therapy. This is particularly exciting due to fact that we are starting treatment at a more clinically useful time point than is the case for most experimental SCI therapies. Moreover, this analytical approach offers a general strategy for examining the robustness of experimental therapies.

Appendix 3

NEW YORK STATE SPINAL CORD INJURY RESEARCH BOARD

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5 Service Commenced During 2024