



SPINAL  
CORD  
INJURY  
RESEARCH  
BOARD

NEW YORK STATE  
DEPARTMENT OF HEALTH

**Annual Report**

January 1, 2010 to December 31, 2010

4/15/11



**NEW YORK STATE SPINAL CORD INJURY RESEARCH BOARD**  
**Roster of Members**  
**As of December 31, 2010**

**Lorne Mendell, Ph.D., Chair**

Stony Brook University, State University  
of New York

**Donald S. Faber, Ph.D., Vice Chair**

Albert Einstein College of Medicine at  
Yeshiva University

**Allen L. Carl, M.D.**

Albany Medical Center

**Jeffrey D. Ehmann**<sup>1</sup>

**Brooke M. Ellison, M.A.**

The Brooke Ellison Project

**Michael E. Goldberg, M.D.**<sup>1</sup>

Columbia University College of Physicians  
and Surgeons

**Jason H. Huang, M.D.**

University of Rochester Medical Center

**Gary D. Paige, M.D., Ph.D.**

University of Rochester Medical Center

**Paul Richter**

Spinal Cord Society

**Adam B. Stein, M.D.**

The North Shore-Long Island Jewish  
Health System

**Robert D. Trotta, Esq.**

Davis and Trotta, Attorneys-at-Law

**Jonathan R. Wolpaw, M.D.**

Wadsworth Center  
New York State Department of Health

<sup>1</sup> appointed during 2010

**New York State Department of Health Staff  
Wadsworth Center  
Extramural Grants Administration**

**Bonnie Jo Brautigam**  
Executive Secretary to the Board and Director

**Teresa K. Ascienzo**  
Associate Accountant

**Lani Rafferty**  
Health Program Administrator 2

**Mary Ryther**  
Health Program Administrator 1

**Nora Prall**  
Administrative Aide

# Executive Summary

More than 600 New York residents suffer traumatic spinal cord injuries (SCI) each year, joining the estimated 80,000 New Yorkers who are living with paralysis and other effects of SCI. The personal and economic costs to persons with this debilitating condition, their families and to society are immense.

SCI results in a sudden change in the quality of life for those affected, and those with SCI are often young. Injuries can be caused from vehicle, diving or sports accidents, from falling down stairs or from violent acts. 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 constant pain.

The economic costs of SCI are great. In addition to medical care and loss of productivity, those with SCI incur significant costs for home and vehicle modifications, equipment purchase, medications and personal assistance services. The Institute of Medicine of the National Academies reports that first year costs for an individual with SCI range from approximately \$10,000 to \$700,000, with annual costs thereafter ranging from approximately \$14,000 to \$122,000.<sup>1</sup>

The New York State Spinal Cord Injury Research Board (SCIRB or Board) was created in 1998 to oversee and support proposals from leading New York State researchers in their efforts to find a cure for SCI. To fund this research, the Spinal Cord Injury Research Trust Fund (Trust Fund) was established, financed primarily by surcharges on moving traffic violations, since automobile accidents are a major cause of SCI.

This state-sponsored program is the largest in the nation; New York's investment in SCI research has stimulated millions of dollars in additional funding for New York State researchers from sources such as the National Institutes of Health, the Department of Veterans' Affairs, the Craig H. Neilsen Foundation, the Christopher and Dana Reeve Foundation and the Department of Defense, among others.<sup>2</sup> The number of National Institutes of Health (NIH)-funded SCI research awards made to New York State researchers grew from 9 in 1998 to 32 in 2009 (the last year for which reporting is considered complete).<sup>3</sup> At least 18 spinal cord injury-related patent applications have been filed by New York State researchers since 2001.<sup>4</sup> These data reflect a significant and sustained stimulus to the state's economy as a result of its investment. Moreover, the scientific advancements of New York State's research community are leading to a better quality of life for its injured citizens and their families.

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<sup>1</sup> Institute of Medicine of the National Academies. "Spinal Cord Injury – Progress, Promise, and Priorities." 2005. The National Academies Press.

<sup>2</sup> As reported by SCIRB-funded contractors to the Chair of the Board in 2010.

<sup>3</sup> National Institutes of Health, Research Portfolio Online Reporting Tools, search limited to "spinal cord injury."

<sup>4</sup> United States Trade and Patent Office on-line search, search limited to "spinal cord injury."

Fiscal challenges in New York State necessitated the elimination of approximately \$16.2 million in funding for a host of promising new research projects in 2010. Specifically, 10 award recommendations were unable to be funded and applications received in response to two Requests for Applications were unable to be independently reviewed for scientific merit by a panel of experts. Among them were requests to expand the activities of the Richter Center of Research Excellence and to recruit promising new investigators to New York, establishing new robust research programs, some of which would have served as mechanisms to obtain additional funding from federal agencies and private foundations.

The Board is grateful to the Governor and the Legislature for the funding provided to date and looks forward to additional support for such highly meritorious SCI research in the coming years. The salient accomplishments of the Board and Program during 2010 include:

- Twelve Board members were seated as of December 31, 2010; one position remains vacant.
- During 2010, as a result of SCIRB funding, 32 journal articles were published or accepted for publication; 63 abstracts from SCIRB-funded projects were presented at scientific meetings and symposia (Appendix III); and 2 new patent applications were reported (Appendix VI).
- Thirty-six SCIRB-funded research grants were active in 2010.

With over a decade of support from this program, New York State researchers are entrenched in ground-breaking SCI research. Researchers here made significant accomplishments in 2010 to better-understand basic biological processes that occur in SCI, the mechanisms associated with the repair of the spinal cord and to translate those findings to clinical applications. Some highlights include:

**Dr. Christopher Henderson**, Columbia University, has screened more than 50,000 chemical compounds for small molecules that promote axon regrowth. From this large-scale screen, four novel compounds with potent activity on axonal regeneration were identified. These compounds will not only provide new molecular insights into the process of axonal regeneration on myelin, but also hold the potential to be developed into “lead compounds” for future therapeutic uses in the treatment of SCI. For further information, see page 10.

After SCI, axon loss is thought to be worsened by the destruction of myelin, the protective coat that normally surrounds nerves. Myelin is not only necessary to protect nerves from degeneration, but also for nerve signals to be transmitted. Without myelin, therefore, nerves that survive initial injury become dysfunctional and are more likely to die during the injury aftermath. **Dr. Holly Colognato**, Stony Brook University, State University of New York (SUNY), has been studying enzymes in the SCI environment to determine whether their presence or absence can affect digestion of glial scar proteins that inhibit both axon regrowth and remyelination. A combination of two enzymes has been identified that acts synergistically to overcome growth inhibition properties of the injury scar. For further information, see page 13.

The laboratory of **Dr. Blair Calancie**, Upstate Medical University, SUNY, is developing new methods using a variety of growth-enhancing molecules for treating injury to the nerve roots at the base of the spinal cord, known as the *cauda equina*, and is

assessing the time period over which loss of nerve conduction occurs after this type of SCI. Researchers have found that within 24 hours of injury, nerve conduction in the injury site still occurs, but significant loss of conduction occurs within about 48 hours and within 72 hours of injury there is complete conduction failure. These findings carry important implications for the necessary time course to implement a clinical strategy following an acute *cauda equina* injury in human subjects. For further information, see page 14.

**Dr. John Martin's** laboratory at Columbia University is studying whether increasing the activity of axons in the corticospinal tract that remain intact after SCI by electrical stimulation strengthens their connections and improves motor function. The research has shown that electrical stimulation of spared corticospinal tract axons in rats caused substantial outgrowth of these axons. It also was demonstrated that this corticospinal tract sprouting resulted in stronger connections with spinal motor circuits. Further, it was determined that electrical stimulation of the corticospinal system led to restoration of skilled forelimb movement control. By contrast, non-stimulated animals did not recover function, and minimal corticospinal tract sprouting was observed. This provides strong scientific evidence that activity can be harnessed to repair the damaged corticospinal tract and promote skilled motor functions. This strategy can be translated to humans using transcranial magnetic stimulation or transcranial direct-current stimulation. For further information, see page 19.

At present, few treatments are available for SCI patients, and designing novel combinatorial therapies based on stem cell biology could have high impact in this area. **Dr. Sally Temple's** laboratory at the Regenerative Research Foundation has developed stem cells and slow-release microspheres that could be used to deliver growth factors beneficial to the SCI patient to help repair the spinal cord tissues. For further information, see page 9.

Some SCIRB-funded researchers are utilizing the growing understanding of the cellular processes involved in SCI and repair to develop treatment strategies that address the physical challenges of people living with SCI.

**Dr. William Collins** of Stony Brook University, SUNY, is studying the electrical properties of the external urethral sphincter that may contribute to failure of muscle coordination of the bladder-sphincter that frequently occurs after SCI. This failure of muscle coordination interrupts neuronal connections between the brainstem and the lumbosacral spinal cord, leading to incomplete voiding and urine retention. Understanding the possible role of injury-induced changes in the intrinsic electrical properties of external urethral sphincter motoneurons should provide a new model for understanding the etiology of bladder-sphincter loss of muscle coordination and for development of effective new therapies. For further information, see page 26.

Brain-machine interface (BMI) systems allow some people who are paralyzed, such as those with SCI, to interact with the world. Using the world's first BMI that controls the forces the user intends to output, **Dr. Joseph Francis'** laboratory at Downstate Medical Center, SUNY, is studying monkeys making reaching movements while wearing an exoskeletal robotic system. Neural activity from the brain regions involved in motor control was recorded to identify which portions of the cortex code for various visual, somatosensory and motor components of such reaching/transporting tasks.

This “mapping” will be extremely useful to those with SCI as more is learned about how the brain controls movement. For further information, see page 31.

A centerpiece of the research efforts is the Richter Center of Research Excellence (CORE), designed to integrate four large research projects to develop multi-modality treatments for acute and chronic SCI.

Under the leadership of **Dr. Rajiv R. Ratan**, Winifred Masterson Burke Medical Research Institute, the CORE made significant progress toward developing treatments that combine drug therapy with robotics-enhanced rehabilitation and cellular transplantation. Results from high throughput screening of 2000 previously FDA-approved drugs and nutraceuticals has yielded 30 candidates that enable axon growth on inhibitory substrates and novel screening methods. Of these, L-DOPA and lithium are excellent translational candidates. Research results suggest that the same inhibitors and their receptors that are thought to play a role in impeding regeneration may also coordinate structural and functional neuronal plasticity in central nervous system health and disease; thus, understanding their role is essential in order to design therapeutic approaches. Additional CORE studies showed that a specific set of cells promotes extensive recovery from SCI in rats and humans. They developed a panel of markers for quality control studies of this promising therapeutic strategy. Further, after developing an interactive robot technology and applying it in a clinical rehabilitation setting, patient progress indicated that robotic therapy is an effective and viable alternative to standard physical therapy, and when used in combination, can improve the quality of life for persons with SCI.

Support for these groundbreaking research projects is key to discovering treatments and cures, increasing the quality of life and reducing the high costs for those affected with SCI and their families. The field of SCI research has grown in the past 30 years from a relatively small endeavor outside the main stream of modern neuroscience research to a major enterprise, well accepted by neuroscience researchers. Significantly, the basic science carried out by researchers in this field, much of it 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. SCI used to be thought of as incurable; although it is not yet possible to reliably repair the human spinal cord, there are modalities of treatment that improve the lives of SCI patients, and continued scientific explorations offer hope for doing more. The Board appreciates the opportunity to serve the citizens of New York State by focusing on this important public health problem while stimulating economic growth through discovery, and hopes to continue those efforts in the coming years.

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# **State of New York Spinal Cord Injury Research Board Annual Report January 1, 2010 to December 31, 2010**

## **I. INTRODUCTION**

More than 600 New York residents suffer traumatic spinal cord injuries (SCI) each year, joining the estimated 80,000 New Yorkers who are living with paralysis and other effects of SCI. The personal and economic costs to these persons, their families and to society are immense.

In July 1998, the Spinal Cord Injury Research Board (SCIRB or Board) and the Spinal Cord Injury Research Trust Fund (Trust Fund) were authorized by legislation enacted under Chapter 338 of the Laws of 1998. This statute added Title IV (Sections 250 through 251) to Article 2 of the Public Health Law and Section 99-f to Article 6 of the State Finance Law. A technical amendment to the provisions of the State Finance Law was enacted in December 1999 by Chapter 612 of the Laws of 1999. The Board's enabling legislation is found in Appendix I to this document.

The Board was first convened in August 1999. The Board is responsible for advising the Commissioner of Health regarding the oversight of a program to support research proposals from leading New York State researchers in their efforts to find a cure for SCI, financed by the Trust Fund. The Board is required to report annually to the Governor and Legislature on its grant-related activities, the status of supported research and on the Trust Fund.

The Board's major responsibilities are to:

- ❖ Develop general policies and procedures for soliciting and selecting meritorious proposals to be recommended to the Commissioner of Health for funding. To meet this responsibility, the Board must undertake the following tasks:
  - Develop funding mechanisms and establish award amounts to stimulate creativity in the investigation of SCI; encourage development of new research programs in SCI; and maximize the unique resources and capabilities available in New York State for advancing the Board's mandate.
  - Identify research areas of emphasis to address existing knowledge gaps or underexplored topics; and ultimately, find a cure for SCI.

- Establish objective merit (peer) and programmatic review processes to identify projects with the greatest potential to impact SCI and its effects; and foster the entry of new neurologic and neuroscience investigators into areas or disciplines with potential to reverse the consequences of SCI.
- ❖ Report annually to the Governor and the Legislature on oversight of the Trust Fund and the progress of Board-sponsored research programs.

This report summarizes the Board's twelfth year of operation and progress to date in fulfilling its mandate.

## **II. BOARD ORGANIZATION AND MEMBERSHIP**

The Board's membership is comprised of 13 members appointed by the Governor and legislative leaders; brief biographies of each member follow. The composition of the Board's current 12 members is approximately 50 percent basic science researchers, 30 percent clinicians and surgeons and 20 percent spinal cord-injured persons or advocates. Members serve four-year terms. One Board seat was vacant as of December 31, 2010.

### ***Board Members***

#### **Lorne Mendell, Ph.D., Stony Brook University, State University of New York (SUNY); Chair**

Dr. Mendell serves as Distinguished Professor in the Department of Neurobiology and Behavior at Stony Brook University, SUNY. He earned a Ph.D. degree at Massachusetts Institute of Technology, did postdoctoral research at Harvard Medical School and taught at Duke University before coming to Stony Brook. His research laboratory focuses on the effects of growth factors known as neurotrophins on the function of spinal circuits. This work expands upon his long-term interest in neuroplasticity of the spinal cord, which is concerned with the ability of spinal cord circuits to be modified. The goal of his current research is to uncover how neurotrophins can improve the function of neural circuits that survive after SCI. In the recent past, his research has dealt with the effect of neurotrophins on pain circuits and segmental reflex pathways. Dr. Mendell is the author of numerous journal articles. His work is supported by the National Institutes of Health (NIH) and the Christopher and Dana Reeve Foundation. He has served in many leadership positions in his field, including as departmental chair at Stony Brook University, editor-in-chief of the *Journal of Neurophysiology* and president of the Society for Neuroscience.

Dr. Mendell has served the Board since June 2004.

**Donald S. Faber, Ph.D., Albert Einstein College of Medicine; Vice Chair**

Dr. Faber has served as chair of the Department of Neuroscience and director of the Rose F. Kennedy Center at the Albert Einstein College of Medicine in the Bronx since 1999. He is a world-renowned neuroscientist who has made major contributions to understanding the regulation and plasticity of synaptic transmission, the role of intrinsic membrane properties in normal and abnormal operation of neural networks, as well as the physiological consequences of nerve cell responses to injury.

Dr. Faber earned a Ph.D. in physiology in 1968 from SUNY at Buffalo. After completing a postdoctoral fellowship with Nobel Laureate John Eccles, he worked as a research associate at the Max Planck Institute for Brain Research in Frankfurt, Germany, and at the Hospital Salpetriere in Paris, France, before returning to this country to join the faculty of the University of Cincinnati in 1972. He then moved to the Department of Physiology at the University at Buffalo, SUNY, in 1974, where he was named an associate professor and director, Division of Neurobiology, in 1978, and rose to the rank of professor in 1981. In 1992, he went on to the Hahnemann School of Medicine (now Drexel University College of Medicine) as chair of the Department of Neurobiology and Anatomy and a member of the School's SCI Program; he then joined the Albert Einstein College of Medicine in 1999. Dr. Faber has served as consultant to the NIH and the National Science Foundation and on the editorial boards of three major journals. His extensive professional recognition is exemplified by his appointment as a Javits Investigator of the NIH National Institute of Neurological Diseases and Stroke and election as a Fellow of the American Association for the Advancement of Science.

Dr. Faber has been serving the Board since June 2007.

**Allen L. Carl, M.D., Albany Medical Center**

Dr. Carl came to Albany after medical training at the University at Buffalo, SUNY, postgraduate experience in orthopedics at New York University-Bellevue Hospital in New York City and SCI training at the University of Toronto, Canada. He has served on the staff at Albany Medical Center for more than 20 years, where he is a professor of orthopedic surgery and pediatrics. Spine disease and disorders became his primary areas of interest, as he perceived these fields to be the last frontiers for innovative medical development. His interest in contributing to the knowledge base in the field of the spine prompted his association with an academic medical center in Albany. In the Capital District, he has collaborated with colleagues at Rensselaer Polytechnic Institute, the General Electric Company and University at Albany, SUNY. From these successful associations, surgical navigation, new metal implants for scoliosis correction and the spinal fusion technique have been developed. Under the direction of Dr. Carl, SCI biomechanics, as a model for neurological repair, has been instituted and studied in his research laboratory through generous donations from the Jeffrey Schneider Spinal Cord Research Program.

Dr. Carl has been serving the Board since December 1998.

### **Jeffrey D. Ehmann**

Mr. Ehmann is a 48 year-old survivor of a 2005 climbing accident that left him a paraplegic. He continues to work fulltime for the media conglomerate Gannett, parent company of USA Today and six New York State newspapers. Gannett is based in McLean, Virginia; Mr. Ehmann telecommutes from his home in Kingston, New York. Mr. Ehmann performs household chores, drives and exercises, hoping to reach his pre-accident fitness level. He is married and has three college-aged children.

Mr. Ehmann was appointed to the Board in February 2010.

### **Brooke M. Ellison, M.A., The Brooke Ellison Project**

In 1990 at the age of 11, Brooke was stricken in an accident that left her paralyzed from the neck down and dependent on a ventilator to breathe. However, Brooke never allowed her physical condition to stand in the way of what she could achieve, and she graduated with honors from Harvard University in 2000 and from Harvard's Kennedy School of Government in 2004. In 2002, Brooke published an autobiography, "Miracles Happen," which was later made into a motion picture directed by Christopher Reeve. For more than a decade, Brooke has worked throughout the country as a public speaker, delivering her message of hope, optimism and strength in the face of obstacles, with her own experiences as a vehicle to convey the message.

Ms. Ellison has worked as an advocate for stem cell research for nearly a decade. In 2006, Brooke ran as a candidate for the New York State Senate, focusing on the need for the state to commit funding to stem cell research. Brooke has continued her work in the field of stem cell research, and in July 2007 she formed a nonprofit organization, The Brooke Ellison Project, to educate and mobilize the public on behalf of stem cell research. Moreover, in collaboration with leading scientists and advocates in the field, Brooke is now working on a documentary to disseminate information for advancing stem cell research.

Ms. Ellison has served the Board since June 2007.

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

Dr. Goldberg is the David Mahoney Professor of Brain and Behavior in the Departments of Neuroscience, Neurology, Psychiatry and Ophthalmology at Columbia University College of Physicians and Surgeons, and Director of the Mahoney Center for Mind and Brain. He is also a member of the Kavli Institute for Brain Science at the Columbia University. He is a Research Scientist at the New York State Psychiatric Institute, and Senior Attending Neurologist at New York Presbyterian Hospital. Dr. Goldberg is currently the President of the Society for Neuroscience.

In 1963, Dr. Goldberg received an A.B. degree, *magna cum laude*, from Harvard College. From 1963 to 1964, he was a graduate fellow at Rockefeller University, and earned a medical degree from Harvard Medical School, *cum laude*, in 1968. He was Medical House Officer at Peter Bent Brigham Hospital from 1968-1969, Research Associate in the Laboratory of Neurobiology and the National Institute of Mental Health from 1969-1972 and Resident in Neurology in the Harvard Longwood Program from 1972-1975.

Dr. Goldberg's research on cognitive systems and neuroscience focuses on the psychophysics and physiology of cognitive processes in the monkey, using single unit recording, iontophoresis and careful behavioral measurements. Current projects include elucidation of the cortical representation of oculomotor proprioception, using saccadic adaptation to understand the coordinate system of neurons in the lateral intraparietal area (LIP), the role of prestriate cortex in visual search and the role of inhibition in the response of parietal neurons. Recent discoveries in Dr. Goldberg's laboratory include the demonstration of a predictive relationship of parietal activity to both saccadic reaction time and visual attention; the demonstration that the lateral parietal area acts as a linear summing junction for at least three independent signals: a saccadic signal, an undifferentiated visual signal, and a cognitive signal; and the proprioceptive representation of eye position in monkey area 3a of the primary somatosensory cortex. He served as president of the Society for Neuroscience from 2009 through 2010.

Dr. Goldberg was appointed to the Board in February 2010.

#### **Jason H. Huang, M.D., University of Rochester Medical Center**

Dr. Huang is chief of the Neurosurgery Department at Highland Hospital and assistant professor of neurosurgery at the University of Rochester Medical Center, where he also directs the neurotrauma and peripheral nerve surgery programs. He is author or co-author of 75 peer-reviewed articles, abstracts, editorial reviews and book chapters. In 1994, he received a bachelor's degree, *magna cum laude*, in the neurosciences from Amherst College. Dr. Huang earned his medical degree in 1999 from Johns Hopkins University School of Medicine. He underwent neurosurgery residency training at the University of Pennsylvania from 1999 to 2006, and was the recipient of numerous awards, as well as NIH grants, during his training. Dr. Huang's main research interest lies in the field of central nervous system injury and repair. He is a faculty member at the Center for Neural Development and Disease at the University of Rochester Medical Center and leads an active extramurally-funded research laboratory. Dr. Huang also is a U.S. Army Reserve neurosurgeon and was deployed to Balad Theater Hospital in Iraq in 2008 during Operation Iraqi Freedom. He received an Army Commendation Medal for his work in treating U.S. soldiers injured with brain and spinal trauma.

Dr. Huang has served the Board since June 2007.

#### **Barbara S. Koppel, M.D., Metropolitan Hospital Center**

Dr. Koppel is chief of neurology at Metropolitan Hospital in New York City and professor of clinical neurology at New York Medical College. She also holds appointments at Terence Cardinal Cook Hospital, Catholic Medical Center of Brooklyn and Westchester Medical Center. In 1978, she earned a medical degree from the College of Physicians and Surgeons of Columbia University in New York City, and completed a residency in neurology at the Neurological Institute, Columbia Presbyterian Medical Center, from 1979 to 1982. Dr. Koppel is the author of numerous journal articles, book chapters and abstracts. She is a member of

the American Academy of Neurology, American Epilepsy Society, New York Academy of Sciences and American Neurological Association.

Dr. Koppel served the Board from June 2001 to February 2010.

### **Gary D. Paige, M.D., Ph.D., University of Rochester Medical Center**

Dr. Paige received his undergraduate education in 1970 from the University of California at Irvine in the biological sciences. He then was accepted to the University of Chicago's Medical Scientist Training Program, where he completed medical school (M.D., 1980) and graduate training in the physiological and pharmacological sciences (Ph.D., 1981). He followed with an internship at Michael Reese Hospital in Chicago and a residency in ophthalmology at the University of California at San Francisco in 1985. Dr. Paige then joined the faculty of Washington University, St. Louis, in the Department of Otolaryngology, where he established and directed the Vestibular and Oculomotor Laboratory. In 1990, he was recruited by the University of Rochester, Department of Neurology, as chief of the Sensory-Motor Neurology Unit, as well as director of the Balance and Eye Movement Laboratory and the Balance Disorders Clinic. In 1998, he was appointed Killian J. and Caroline F. Schmitt Professor and chair of the Department of Neurobiology and Anatomy at the University of Rochester. He has served as director of the Center for Navigation and Communication Sciences at Rochester University since 2002.

Dr. Paige's research on multisensory interactions underlying spatial orientation focuses on how the brain integrates sensory inputs from the outside world (vision and audition) with the internal senses (vestibular and somatosensory) to accurately depict spatial orientation, motion and behavior. He also is interested in how plastic mechanisms register errors and adaptively adjust or restore performance in response to the challenges of development, disease and natural aging. In addition to research and clinical responsibilities, Dr. Paige's academic activities extend to medical and graduate education, peer-review activities for NIH and other research funding agencies, as well as journal review and editorial duties. Dr. Paige has served on the governing boards of the Association of Medical School Neuroscience Department Chairs (as president) and at present is vice president of the Society for the Neural Control of Movement.

Dr. Paige has served the Board since June 2007.

### **Paul Richter, Spinal Cord Society**

In 1973, Mr. Richter was serving as a New York State Trooper Zone Sergeant when he was shot three times and sustained a SCI. Since that time, he has been an avid advocate for those with SCI. For many years, Mr. Richter volunteered to counsel other SCI survivors and instituted an annual fundraiser to raise hundreds of thousands of dollars to fund research for finding a cure for SCI. He is an active member of the Spinal Cord Society.

Mr. Richter identified the need to create a source of funds to support SCI research. Through research, networking and perseverance, he received support from the New York State Legislature to draft a bill, and in 1998, legislation was enacted creating SCIRB and the Trust Fund.

In 2009, the Burke Rehabilitation Hospital and Burke Medical Research Institute in White Plains, New York, honored Mr. Richter as the recipient of the Burke Award, the highest honor bestowed by Burke and its board of directors. The award is presented to an individual or group for strength in overcoming a disability, for establishment of science and research programs concerning disability and for contributions to the development of rehabilitation therapies. Some past recipients of the award include Christopher Reeve and Dr. Howard A. Rusk, considered to be the founder of rehabilitation medicine.

Mr. Richter has served the Board since November 1998.

### **Adam B. Stein, M.D., North Shore-Long Island Jewish Health System**

Dr. Stein completed his medical degree at the New York University School of Medicine in 1987, and residency training in physical medicine and rehabilitation at New York University-Rusk Institute in 1991.

Dr. Stein is chair of the Department of Physical Medicine and Rehabilitation at North Shore-Long Island Jewish Health System. Since 2008, he has been responsible for delivery of rehabilitation services to the system's many hospitals and outpatient therapy centers. He also oversees the system's residency training program in physical medicine and rehabilitation. Previously, Dr. Stein served on the faculty at Mount Sinai School of Medicine in the Department of Rehabilitation Medicine. At Mount Sinai, he directed the SCI Unit and developed a program for ventilator-dependent individuals, while establishing a national reputation in the area of SCI medicine. He has been a co-investigator and key component of the Mount Sinai SCI Model System. He has participated in multiple SCI clinical trials, including those evaluating therapies using monosialotetrahexosylganglioside (also known as GM-1 ganglioside), 4-aminopyridine and autologous activated macrophages. He also has served as program director of Mount Sinai's residency training programs in physical medicine and rehabilitation and SCI medicine. Dr. Stein is a member of both the American Spinal Injury Association and the American Paraplegia Society. He has worked on numerous American Spinal Injury Association committees and has published extensively on many SCI clinical topics.

Dr. Stein was appointed to the Board in September 2009.

### **Robert D. Trotta, Esq., Davis and Trotta, Attorneys-at-Law**

Mr. Trotta is a graduate of Hobart College in Geneva, New York, and Syracuse University College of Law. He is admitted to the New York State Bar, and has worked with the firm Davis and Trotta since 1966. He served in the Dutchess County Public Defender's Office from 1968 to 1981, and worked as Town Attorney for the Town of Northeast for 17 years and School Attorney for the Webutuck, New York Central School District for 4 years. He became interested in finding a cure for SCI after his son, David, was paralyzed from the neck down as the result of a motorcycle accident.

Mr. Trotta has served the Board since May 2005.

## **Jonathan R. Wolpaw, M.D., Wadsworth Center, New York State Department of Health**

Dr. Wolpaw is a board-certified neurologist who has worked at the Wadsworth Center since 1980. He received a medical degree from Case Western Reserve University in 1970, and then completed a residency in neurology at the University of Vermont and fellowships in neurophysiological research at the NIH. He is chief of Wadsworth's Laboratory of Neural Injury and Repair and a professor in the Department of Biomedical Sciences, University at Albany, SUNY.

Dr. Wolpaw's major research interest is developing and using operant conditioning of spinal reflexes as a new model for studying learning and memory in the vertebrate nervous system. He and his collaborators are applying this work to the study of SCI and to development of new treatment methods. Dr. Wolpaw also is designing electroencephalogram (EEG)-based brain-computer interface technology as a new communication and control mode for those with severe motor disabilities. He is the author of numerous journal articles and holds several NIH grants; his research group has received several national and international awards in recognition for their work.

Dr. Wolpaw has served the Board since May 1999.

### **III. BOARD OPERATIONS**

#### ***Staff Support***

The Department of Health Executive Secretary to the Board is Ms. Bonnie Jo Brautigam. The Department of Health liaison to the Board is Ms. Lani Rafferty.

#### ***Meetings***

Meetings are announced at least two weeks in advance and are open to the public. A recording of each meeting is available via the Department of Health's public Web site <http://www.health.state.ny.us/events/webcasts/archive/> for 30 days after a meeting, opening the proceedings to a wide audience. All Board meeting agendas and approved minutes are available by request from the Board's Executive Secretary. Meeting agendas are also posted on the Wadsworth Center's Web site at: <http://www.wadsworth.org/extramural/spinalcord/>.

The State of New York experienced an unprecedented fiscal crisis, and in 2010 the SCIRB budget was reduced, severely limiting program activities to previously contracted research. Recommendations made by the Board to award additional contracts were unable to be considered for contracts, and all activity to consider meritorious research applications was halted.

During 2010, the Board held two meetings on December 3, 2010, at Wadsworth Center's Biggs Laboratory in Albany. During the first meeting, the Board reviewed the draft 2010 Annual Report and voted to approve it with the recommended changes.

Three members of the public were present; two made public statements. Mr. Terry O'Neill, Esq., of the Constantine Institute commented that as a result of war activities, the public is more aware of traumatic brain injury and SCI and thus he believes there is public support for SCIRB. He discussed ways he plans to make sure the Governor and Legislature are aware of funded research successes. Among those successes, Mr. O'Neill stated that research from

SCIRB allowed Acorda Therapeutics, a New York pharmaceutical company, to get a drug approved he was told is “worth \$1 billion per year.” For a full transcript of Mr. O’Neill’s comments, see Appendix V.

Nurit Kalderon, Ph.D. raised concerns about the peer review of an application for funding that she submitted in 2005. Her comments were based on a written statement provided to the Board (see Appendix V).

### ***Bylaws***

No changes were made to the Board’s bylaws in 2010. The bylaws are found in Appendix II.

## **IV. PROGRAM FUNDS**

Through December 31, 2010, cash deposits to the Trust Fund totaled \$76.5 million. Interest on unexpended funds rose to almost \$5.3 million, for a total of \$81.8 million in available cash since the inception of the Trust Fund.

Cash disbursements from the Trust Fund include: voucher payments for research contracts (\$53.8 million); payments for peer-review/miscellaneous contracts (\$2.6 million); and administrative costs (\$3.5 million) over the life of the Trust Fund, as well as a 2002 budgeted cash reduction of \$13.5 million from the Trust Fund, resulting in a cash balance of \$8.3 million as of December 31, 2010.

Remaining liabilities for current research contracts equal approximately \$10.7 million.

## **V. MAJOR ACTIVITIES OF THE BOARD AND PROGRAM**

### ***Peer Review of Research Applications***

With the annual appropriation of up to \$8.5 million until State Fiscal Year 2010/2011, the New York State SCI Research program was the largest source of public funding for SCI research in the nation, aside from the NIH. The Board and staff carefully manage the Trust Fund, ensuring that only the most meritorious research is funded. Applications are received by the Department of Health in response to Requests for Applications (RFAs). Funding recommendations are primarily based on the results of an independent peer review of the scientific merit of each application for funding. This peer review is conducted for the Department of Health through a multi-year contract with the Constella Group, LLC.

The 2010 enacted State Budget did not provide funding for new research projects or peer review. Contracts for 10 awards made in 2009 as a result of the RFA for Collaborations to Accelerate Research Translation (CART) Awards; Innovative, Developmental or Exploratory Activities (IDEA) Awards; Postdoctoral Fellowships; Mentored Research Scientist Development Awards; and Mentored Clinical Scientist Development Awards, totaling approximately \$6 million, were not able to be executed.

Applications received in response to the following RFAs were unable to be peer reviewed:

- Promoting Recruitment of New Spinal Cord Injury Researchers in New York State, \$3.6 million.
- Richter Center of Research Excellence, \$7.2 million.

Further, the plan to develop a biennial scientific meeting of all SCIRB-funded researchers was suspended.

***Importantly, funding for contracts executed prior to April 1, 2010, has continued by virtue of the reappropriation of prior years' funding, and many important and exciting results have stemmed from that work. The remainder of this report addresses those activities.***

***Presentations, Publications and Patents Resulting From SCIRB-Funded Research***

During 2010, investigators reported 32 journal articles were published or accepted for publication; 63 abstracts from SCIRB-funded projects were presented at meetings and symposia (Appendix III); and two new patent applications were submitted (Appendix IV).

***Research Projects and Accomplishments***

Highlights of research accomplishments related to ongoing SCIRB-funded grant contracts follow:

**Collaborations to Accelerate Research Translation (CART) Awards**

**C020922, Sally Temple, Ph.D.**, Regenerative Research Foundation (formerly at Albany Medical College), “Engineering Embryonic Spinal Cord Stem Cells for SCI Repair,” January 1, 2006 – December 31, 2010; \$1,268,451.

After SCI, loss of spinal cord cells and damage to sensory and motor tracts leads to paralysis. Successful treatment of SCI will most likely include cell transplantation to replace damaged or lost spinal cord cells and growth factors that will help with cell survival and repair of severed tracts. Previous research conducted in this laboratory has produced embryonic spinal cord stem cells that can be beneficial for SCI. Implanted stem cells in the SCI zone do not have access to growth factors that are needed for them to develop efficiently into useful spinal cord cells. To direct the implanted stem cells, they need to be provided with growth factors over long periods of time.

Investigators have demonstrated that embryonic spinal cord cells can be easily engineered to produce high levels of the growth factor IGF-1 and showed that these cells promoted the outgrowth of motor axons. Transplantation of these cells into a mouse model of SCI led to a minor behavioral improvement. Further, multipotent adult progenitor cells promoted regeneration of injured axons when transplanted in SCI animals.

Biodegradable microspheres that incorporated growth factors like sonic hedgehog growth factor (Shh) were generated. These microspheres were non-toxic and capable of prolonged release of biologically active growth factors. The investigators demonstrated that

administration of biodegradable microspheres releasing Shh resulted in significant functional improvement in two different mouse models of SCI: contusion and dorsal hemisection.

The developed stem cells and slow-release microspheres could be used to deliver growth factors beneficial to the SCI patient to help repair damaged spinal cord tissues. There are currently few treatments for the SCI patient, and developing novel therapies based on stem cell biology could have high impact for SCI patients.

**C020923, Christopher E. Henderson, Ph.D.**, Columbia University, "Screening for Small Molecules With Activity in CNS Regeneration," January 1, 2006 – December 31, 2009; \$953,287.

One of the major hurdles preventing regeneration following SCI is the very slow spontaneous regrowth of injured nerve fibers, called axons, in the hostile environment of the damaged adult central nervous system (CNS). Various strategies are being undertaken to overcome this impediment, including attempts to block the inhibitory molecules expressed by other cells in the spinal cord. A complementary approach was pursued: attempting to identify chemical compounds that can boost the ability of neurons to grow axons, even in the presence of inhibitory molecules.

Three laboratories collaborated on this project: one with experience in creating cell models of the regeneration process, one with expertise in medicinal chemistry and drug screening and one with a robotic platform that allows high-throughput screening of chemical libraries containing tens of thousands of compounds for their ability to trigger axonal regeneration in the culture dish. The overall objective of the project was to identify chemical compounds that affect axonal growth under these conditions. Many of the compounds were expected to offer new insights into the molecular mechanisms underlying regeneration. A smaller number of compounds, perhaps one or two, would have suitable properties for further development as drug candidates.

After four years of work, the project has been successfully completed. An effective, cell-based, high-throughput assay system has been established as the cell model for SCI. This system enabled screening of more than 50,000 chemical compounds for small molecules that promote axon regrowth on the inhibitory myelin-associated glycoprotein substratum. From this large-scale screen, four novel compounds with potent activity on axonal regeneration have been identified. Most prominently, all four lead compounds have shown good drug-like properties, and for three of the four, potential targets already have been identified.

The four lead compounds identified from the screen will not only provide new molecular insights into the process of axonal regeneration on myelin, but also hold the potential to be developed into drug lead compounds for future therapeutic uses in SCI.

**C020924, John Martin, Ph.D.**, Columbia University Medical Center, “Bypassing Spinal Cord Injury to Promote Motor Function,” January 1, 2006 – December 31, 2010; \$827,667.

SCI interrupts connections between the brain and spinal cord that transmit motor control signals and somatic sensory messages. Typically, SCI leaves the spinal circuits below the lesion intact. This project aims to develop a bridge around an SCI in the cat, based on the investigator’s studies in the rat. To bridge the injury, a spinal nerve that originates above the injury is detached from the muscle it controls, and the severed end is inserted into the lumbar spinal cord caudal to the injury. Motor axons from the bridge nerve grow and form connections with spinal cord neurons.

The researchers have extended their earlier electrophysiological findings showing that bridge nerve electrical stimulation evoked postsynaptic responses in the cat spinal cord and, at short latency, muscle activation. The spinal responses became progressively greater and more phasic during the several-month period of study, suggesting systematic outgrowth of the bridge nerve and strengthening of its connections. Stronger bridge stimulation led to stronger spinal postsynaptic responses and greater electromyographic activity, suggesting that regenerating bridge axons are capable of recruiting spinal neurons. Finally, bridge stimulation also resulted in hind-leg muscle contractions while animals were walking on a treadmill. Taken together, these findings indicate that regenerating bridge axons contact lumbar spinal motor circuits at the insertion site. The plan for upcoming experiments is to implant a stimulating electrode in the brain stem of bridged animals to activate the corticospinal tract. It will be determined whether such stimulation can drive muscle actions caudal to the injury in the cat, as had been shown in the rat. If so, evidence would be provided that the brain’s motor centers could access the spinal bridge circuit to bypass SCI. It also is planned to assess the role of the bridge in recovering voluntary control of locomotion.

In parallel rat experiments, a series of behavioral studies were conducted examining whether a bridged spinal injury using this laboratory’s model leads to improvement in motor function after a complete spinal section. Rats received a full transection at the thoracic vertebrae T13/lumbar vertebrae L1. The bridge nerves were implanted bilaterally, from above to below the transection. Animals were trained using a novel robotic technology. The arm of a haptic robot was used to supply initial hind-quarter postural support, by exerting the necessary vertical lift force to prevent the hind quarters from dragging. During the 20-day survival period, the bridged animals showed a reduction in vertical lift force exerted by the robot, indicating that the spinal cord was now providing more postural support. Using a behavioral measure, the accessory olfactory bulb score, it was also determined that bridged animals expressed more functional hind-quarter control than unbridged controls. These findings indicate that, by means of a bridge nerve, the nervous system can help control movements after a complete spinal cord transection.

**C020925, Jian Kang, Ph.D.** (initially Jane Lin, Ph.D.), New York Medical College, “Bystander Death in Traumatic Spinal Cord Injury,” January 1, 2006 – December 31, 2010; \$1,070,852.

In patients with SCI, a major clinical problem is that tissue damage increases for days after the initial traumatic event. The investigators have found that adenosine triphosphate (ATP) plays three important roles in this secondary injury. First, ATP released through Cx43 hemichannels in the membrane of astrocytes produces adenosine that activates A1 receptors to play a neuroprotective role. Second, ATP activates P2X7 receptors to depolarize neurons

and cause neuronal damage. And third, ATP activates P2Y1 receptors in astrocytes to induce astrocytic glutamate release that causes cell damage.

Dr. Nedergaard has found that deletion of Cx43 is highly neuroprotective in traumatic SCI in a rat model of weight drop injury. The researchers have shown that Brilliant Blue G, a P2X7 receptor antagonist protein, improved functional recovery and reduced tissue injury following SCI in rats.

A set of studies that show that Cx43 hemichannel expression is upregulated after traumatic injury is nearly completed. Finally, the research has demonstrated that human astrocytes are large, structurally more complex and differ functionally from rodent astrocytes.

**C020926, Alexandra Joyner, Ph.D.**, Memorial Sloan-Kettering Cancer Center (formerly New York University School of Medicine), “Genetic and MRI Studies of Spinal Cord Stem Cells,” January 1, 2006 – December 31, 2009; \$1,063,794.

Long-term recovery from SCI is often minimal because minimal replacement of damaged cells occurs in the spinal cord. The investigators hypothesized that an effective therapeutic approach for SCI is to mobilize the resident neural stem cells (NSCs) in the spinal cord to mediate recovery.

The growth factor Shh was studied to determine if it plays a role in regulating adult NSCs in the spinal cord to mediate recovery, using a mouse model and a new, noninvasive micro-MRI to label and follow spinal cord NSCs in response to SCI. The project addresses two primary questions: 1) do NSCs in the adult spinal cord respond to Shh and therefore express the target gene Gli1; and 2) do Gli1-expressing cells have the potential to repair SCI?

To respond to these questions, the Joyner laboratory applied genetic approaches to characterize Gli1-expressing cells in the spinal cord to ascertain whether Shh signaling regulates repair and/or formation of a glial scar, which inhibits SCI repair. In the long term, growth factors could be infused into the spinal cord, and the methods developed could test the growth factors' ability to induce proliferation and migration of neural stem cells to SCI and to promote differentiation to repair the injury functionally.

Dr. Joyner collaborated with Dr. Turnbull's laboratory at New York University, which developed new MRI methods for visualizing and assessing SCI in the mouse, overcoming motion artifacts that obscure the spinal cord and injury site. The Turnbull laboratory also developed methods to magnetically label NSCs, enabling MRI measurements of their migration rates, an important factor in the ability of NSCs to reach injury sites and participate in repair.

Researchers showed that Gli1 identifies SC cells responding to Shh signaling and is induced in a subset of spinal cord astrocytes by Shh in neurons. Further, after SCI, they determined that Shh is not required for gliosis, nor are Gli1-expressing cells induced to proliferate or migrate to the injury site. Results of the studies indicate that Shh signaling normally plays an important role in homeostasis.

The methods and results provide a unique look at SCI and repair processes. Significantly, the results characterized the role of Shh signaling in homeostasis and repair following SCI.

**C020927, Gordon Barr, Ph.D.**, New York State Psychiatric Institute, “Gene Expression After Acute and Chronic Injury and Rescue,” January 1, 2006 – December 31, 2010; \$1,275,529.

Injury to the spinal cord disrupts pathways from the brain downward and impairs use of muscles and sensations from the body below the damage. A rat model was studied to understand the changes in damaged neurons after SCI and ultimately to improve function.

Using microarrays, the laboratory measured gene expression in neurons after descending axons were cut in rats to assess the gene expression changes as the injured neurons recover. The goal was to identify coherent functional groups of altered expression in genes that changed over six weeks after their axons were cut.

The study showed that few changes occurred at 4 hours, but the expression of large numbers of genes changed from 3 days through 42 days. Analysis showed that some families of genes had reduced expression and others had increased expression. In general, early changes were localized to the membrane of the neuron and involved genes for cell-signaling processes. At 7 and 14 days post-SCI, there was increased expression of nuclear transcription factors that regulate other genes and substantial changes related to the axon, decreased metabolism and altered fatty acid synthesis in microtubule genes. At 42 days following lesion, although many changes seen at 7 and 14 days remained, fewer of the internal environment and energy metabolism changes continued, and again, altered gene expression related to the cell membrane and cellular communication was observed. Thus, these data describe detailed sequences of gene expression in cells as they are injured, begin to die or recover over a six-week period after the axons were cut.

In prior studies, transplantation of a peripheral nerve into the site of injury in adult animals has been shown to improve outcomes and rescue motor function. Investigators sought to understand the mechanisms by which this effect occurred. Experiments were conducted in both young and adult animals to define changes in gene expression after lesion and transplant, compared to lesion-alone conditions. It was hypothesized that both transplants and lesions at young ages would produce parallel rescue in neurons damaged by the lesions.

The laboratory found far more changes in gene expression in the transplanted animals and fewer in the young animals. The analysis showed different functional changes in transplanted animals, with the notable exceptions of maintained and even elevated energy-related genes. Thus, in the lesion-only animals, energy/mitochondrial genes briefly increased and then declined until six weeks post-lesion, whereas in the lesion-plus-transplant animals, energy genes maintained or even increased their expression levels. In general, however, gene expression was kept at normal levels in transplanted animals. At present, the “young” animal data are undergoing further analysis.

The implications of these results are that the environment (e.g., a transplant) allows intrinsic cellular functions within the damaged neurons to maintain some level of normalcy. This conclusion implies that if mechanisms exist to support these functions further within a permissive environment, more successful regeneration and increased recovery of function might occur.

**C020929, Holly Colognato, Ph.D.**, Stony Brook University, SUNY, “Remyelination and Spinal Cord Injury,” January 1, 2006 – December 31, 2010; \$1,013,695.

After SCI, axon loss is thought to be made worse by the destruction of myelin, the protective coat that normally surrounds nerves. Myelin is not only necessary to protect nerves from degeneration, but also for nerve signals to be transmitted. Without myelin, therefore, nerves that survive initial injury become dysfunctional and are more likely to die during the injury aftermath. Myelin is produced by specialized glial cells; however, at present it is not known how to stimulate the survival, proliferation or maturation of these glial cells, or how to promote their ability to synthesize myelin following SCI. This project's overall goal is to understand how spinal cord glial cells are regulated by their neighboring cell types and by the proteins they produce in order to devise strategies to promote repair following SCI.

Investigators studied the possibility of stimulating glial cell survival, glial cell division and myelin synthesis by altering proteins in the glial cell environment both in healthy spinal cord and injured spinal cord. To that end, mouse models of SCI in particular were examined to determine whether interactions with certain extracellular matrix proteins and/or immune cells in the injury environment lead to enhanced or slowed recovery following SCI. It was found that signaling molecules, called Wnts, influence the differentiation ability of myelinating glia. Specifically, it was established that Wnt expression changes following SCI, and that Wnt signaling is activated following SCI.

This laboratory has analyzed how extracellular matrix molecules and their receptors influence myelination in the rodent spinal cord. Evaluation of genetically modified mice that lack a specific matrix protein, laminin, showed that laminins regulate multiple stages of myelination, so that myelination is delayed or inefficient in mice lacking the appropriate laminin matrix signals.

Enzymes in the injury environment have been altered using genetically modified mice, as well as by directly adding enzymes to the injury. It was then examined whether the presence or absence of putative modifying enzymes can affect digestion of glial scar proteins known to be inhibitory for both axon regrowth and remyelination. A combination of two enzymes has been identified that acts synergistically to overcome growth inhibition properties of the glial scar. Thus, with proper control of specific proteins and enzymes in the glial cell environment, it may be possible to devise strategies to stimulate myelin production and axon regrowth following SCI.

**C020930, Blair Calancie, Ph.D.**, Upstate Medical University, SUNY, “Repair of *cauda equina* Injury,” January 1, 2006 – December 31, 2010; \$1,202,400.

This project is designed to develop new methods for treating injury to the collection of nerve roots at the base of the spinal cord known as the *cauda equina*. Damage to the spinal column at or below thoracic-level 11 often causes injury to the *cauda equina*. Such injury can result in loss of muscle function in the legs and bladder (paralysis), loss of sensation and at times, chronic burning pain. About one in every five persons admitted to a hospital with SCI actually has sustained *cauda equina* injury. At present, no treatment is available for the nerve damage, and the probability of natural recovery is poor. This laboratory plans to develop an effective treatment using a combination of molecules to encourage nerve growth and reduce scar tissue. These molecules will be delivered through tiny particles called nanospheres that dissolve after placement at the site of injury, slowly releasing their contents.

Studies of the pattern of nerves transversing to muscles in the rat tail have been completed and published (Appendix III, C020930). Investigations of the rate at which the severed nerve endings lose their ability to conduct electrical signals have also been completed. Researchers have found that testing of conduction within 24 hours of injury almost always shows positive results, testing at 48 hours shows failed conduction in about 70 percent of cases and testing at (or beyond) 72 hours shows complete conduction failure. These findings carry important implications for the necessary time course to implement a clinical strategy following an acute *cauda equina* injury in human subjects.

In the past two months, this laboratory finalized development of an injury model that leaves just the distal half of the rat tail paralyzed. With this model now established, studies have begun to assess several repair methods. All these methods utilize guidance channels filled with a variety of growth-enhancing molecules. It is anticipated that some combination of molecules will prove especially effective at promoting nerve re-growth to the tail muscles of the rat. Currently, empty guidance channels are being implanted, and investigators are documenting the extent of recovery in animals subjected to this injury and developing a minimal treatment strategy.

**C020931, Dennis J. Stelzner, Ph.D.**, Upstate Medical University, SUNY, “Local Release of Chondroitinase to Treat Spinal Injury,” January 1, 2006 – December 31, 2010; \$1,085,646.

After SCI, a variety of factors inhibit damaged nerve fibers, or axons, from regrowing, and single treatments to deal with this challenge have had limited success. The investigators’ strategy is to incorporate a variety of therapeutic agents that have had previous success in blocking an inhibitory factor or stimulating a growth response, using very small injectable particles (nanospheres). These nanospheres are made of a polymer that can be fabricated to degrade at different rates and thereby release different agents after a single injection.

The investigators used nanospheres that release the enzyme chondroitinase ABC (cABC) over time. cABC degrades a portion of the glial scar that forms after SCI (chondroitin sulfate proteoglycans, CSPGs) that is inhibitory to nerve (axonal) growth. cABC digests CSPGs, promotes axonal growth and also promotes the migration and maturation of cells that insulate axons (myelin) when placed on CSPGs in culture and after SCI.

To evaluate the effectiveness of cABC delivery methods, the researchers delivered cABC via nanospheres and also with direct injections of cABC enzyme. The research showed that cABC nanospheres release active enzyme which continues to degrade CSPGs for at least two weeks, whereas the amount of degradation decreased after two weeks using enzyme injections. Both delivery methods stimulate axonal growth, but cABC nanospheres degraded CSPGs and promoted axonal growth better than a single cABC enzyme injection.

Using cABC nanospheres is an effective delivery method to degrade CSPGs after SCI and promotes axonal growth and the ingrowth of myelin forming cells into regions of SCI. Moreover, delaying injection of nanospheres/enzyme by two weeks post-SCI still promotes axonal growth increasing the likelihood of clinical use.

Investigators plan to continue their studies, to determine the origin of axons that grow/regenerate after cABC treatment and the distance of growth past SCI; determine if cABC

treatment increases remyelination after SCI; and determine if acute or delayed treatment after SCI enhances recovery of function.

**C020932, Xiang Yang Chen, Ph.D.**, Wadsworth Center, New York State Department of Health, "Using Reflex Conditioning to Restore Spinal Cord Function," January 1, 2006 – December 31, 2010; \$1,074,393.

SCI leads to abnormal spinal reflexes that contribute to motor disabilities. Operant conditioning can change spinal cord reflexes in monkeys, rats, mice and humans, including humans with partial SCI. Reflex conditioning changes locomotor behavior and can improve locomotion in rats with SCI. Thus, spinal reflex conditioning could be an important new method for inducing and guiding spinal cord plasticity to help restore function after SCI. The goals of this project are to further develop operant conditioning of spinal reflexes as a new therapeutic approach and establish its clinical value for humans with SCI.

The researchers used the new lateral column contusion model to assess the effects of H-reflex conditioning on locomotor function in the rat after SCI. They assessed the effects of H-reflex conditioning on GABAergic interneurons and receptors, established the human H-reflex conditioning protocol and are evaluating whether it can improve recovery in patients with partial SCI. Further, they are exploring whether reflex conditioning can affect the functional outcome after peripheral nerve injury and regeneration.

Investigations will continue to define the capabilities, characteristics and long-term efficacy of reflex conditioning and the anatomical and physiological plasticity induced by reflex conditioning. Additionally, studies will be completed to evaluate the effects of reflex conditioning on motor function in people with SCI. Successful completion of this project should introduce a new therapeutic method for restoring function after SCI. When techniques for achieving significant spinal cord regeneration become available, the reflex conditioning protocols that are being developed as part of this project should be valuable, perhaps even essential, for re-educating a restored spinal cord to function effectively.

**C022057, Urs Rutishauser**, Memorial Sloan-Kettering Cancer Center, "Manipulation of Glycans in Repair of Spinal Cord Injury," April 1, 2007 – September 30, 2010; \$ 951,768.

Schwann cells hold significant potential as a cell-based repair strategy for clinical use in humans. However, migration of grafted Schwann cells appears to be limited by their interactions with host astrocytes that encapsulate the lesion epicenter. It is hypothesized that engineered expression of polysialic acid by Schwann cells would promote outward migration of implanted Schwann cells and help facilitate neuronal regeneration. Likewise, polysialyltransferase modification of neurons may enable their re-growing axons to bypass the inhibitory environment of the glial scar, allowing regeneration after SCI.

After completing *in vitro* and contusive SCI work, this laboratory has finished the entire spinal cord transection injury paradigm to address whether neuronal or Schwann cell-mediated polysialyltransferase expression can effect axonal regeneration from axotomized brainstem neurons across an implanted Schwann cells bridge.

The investigations showed that that cell surface modification with polysialic acid in either neurons or implanted glial cells (Schwann cells) can induce axonal regeneration following SCI.

Such a finding can be expected to have significant impact on the field and clinically. Approaches that enhance the effectiveness of Schwann cells, such as gene therapy with polysialyltransferase, could then be taken in future combination clinical forays.

Based on this finding, investigations will continue using a more clinically relevant chronic injury contusion model of SCI.

**C022058, Victor Arvanian**, Stony Brook University, SUNY, “Neurotrophins and Function of the Injured Spinal Cord,” April 1, 2007 – March 31, 2011; \$ 1,203,895.

The objectives of the project are to examine the possibility of re-establishing the functional synaptic connections to individual motoneurons throughout the injury region after lesion and contusion injuries in adult rats. In this study, spinal cord hemisection in adult rats was a suitable model of incomplete injury to investigate whether treatment would establish functional connections around or through the lesion.

To orchestrate re-establishment of functional innervation with lumbar motoneurons after an intervening lateral thoracic hemisection, adult rats were treated with agents (1) Nogo-A antibodies to neutralize the growth-inhibitor Nogo-A; (2) neurotrophin NT-3 (NT-3) via engineered fibroblasts to promote neuron survival and plasticity; and (3) *N*-methyl *D*-aspartate (NMDA) receptor 2d (NR2D) subunit via human simian virus-1 amplicon vector to elevate NMDA receptor function, thereby enhancing synaptic plasticity and promoting the effects of NT-3. Synaptic responses evoked by stimulation above the hemisection were recorded.

In uninjured adult rats, a short-latency, about 1.5 months, monosynaptic response was recorded. After hemisection, this monosynaptic response was abolished. In the group that received all of the agents, a long-latency, about 9 months, polysynaptic response was observed that was not abolished by resection of the spinal cord through the hemisection area. This finding suggests that these novel responses resulted from establishment of new connections around the hemisection. Analysis showed an increased number of axons that re-crossed the midline below the hemisection in that group. Together, these results suggest that the combination of Nogo-Ab+NT-3+NR2D is an effective approach that can produce a functional “detour” around the lesion in a laterally hemisected spinal cord.

Experiments also were conducted using specific behavioral tests to evaluate the motor function and sensory tests. The aim was to determine whether establishing polysynaptic connections in chronically hemisected and treated animals would facilitate recovery of locomotor function. Sensory tests were designed to reveal potential adverse effects arising from the treatment. Statistical analyses will be completed for outcomes from 6 different behavioral tests performed on 60 animals (10 rats per group, 6 groups depending on treatment) at 7 time points post-injury. These results of behavioral evaluation will be combined with the results of electrophysiological and tracing experiments and submitted for publication.

To date, these aims have been successfully accomplished using a lesion SCI model. The next project will determine whether this treatment will induce stronger connections, enhance axonal branching and facilitate recovery of function after contusion injury.

**C023689, Marie Filbin, Ph.D.**, Hunter College, City University of New York (CUNY), “Targeting Soluble AC for the Recovery of Spinal Cord Injury,” October 1, 2008 – September 30, 2012; \$1,440,000.

This laboratory previously showed that if levels of the molecule cyclic adenosine monophosphate (cAMP) are elevated in neurons, the neurons can regenerate in the adult brain and spinal cord. Elevated cAMP increases the presence of the enzyme arginase which is necessary to promote nerve regeneration in animal models of SCI. However, researchers recently found that if cAMP is elevated persistently for a long period, such as with the use of the drug Rolipram, the system becomes desensitized, the levels of arginase decrease and the nerves cease regenerating. Consequently, researchers proposed that intermittent increases, rather than continuous elevation of cAMP, will be more effective in promoting nerve regeneration and found that the system is desensitized, on average, by the seventh day of treatment. The results suggest a treatment schedule which will optimize the cAMP effect on nerve regeneration.

The laboratory also is characterizing a form of the enzyme soluble adenylyl cyclase, which synthesizes cAMP. This enzyme is expressed in nerve cells, and the ability of the drug brain-derived neurotrophic factor, or BDNF, to allow nerve cells to grow in an environment that inhibits growth, is dependent on soluble adenylyl cyclase activity. Preliminary data have been obtained showing that if the levels of soluble adenylyl cyclase are increased in the nerves of the eye, the optic nerve can regenerate after it is crushed.

Finally, researchers have optimized a method to measure the activity of soluble adenylyl cyclase and started a high-throughput screen to identify soluble adenylyl cyclase activators from a library of small molecules. Thus far, over 4,200 molecules have been screened and 4 possible activators have been identified that warrant further testing.

**C023690, Maria Knikou, Ph.D.**, College of Staten Island, CUNY, “Mechanisms Underlying Locomotor Recovery after Step Training in SCI,” October 1, 2008 – September 30, 2012; \$1,422,066.

Locomotor recovery in those with SCI is not well understood. Intensive locomotor training is a major rehabilitation paradigm for recovery of walking function in persons with SCI and is believed to contribute to functional reorganization of spinal neural circuits and specific neuronal pathways. However, the plasticity, or changes in structure and function, of the human spinal cord in response to this intervention are minimally examined and not well understood. Since researchers do not know how locomotor recovery is accomplished, rehabilitation strategies cannot be optimized. This project seeks to investigate the neural mechanisms underlying plasticity of the central nervous system after intensive locomotor training and optimize a therapeutic intervention for recovery of walking in humans after SCI.

Recovery of walking in people with a SCI following intensive robotic locomotor training is likely driven by specific neural circuits in the human spinal cord that are reorganized after training to promote well synchronized leg muscle activity patterns suited to the motor task of walking. Reorganization of neuronal circuits of the injured human spinal cord is examined using noninvasive electrophysiological techniques that measure the behavior of specific spinal neural pathways and circuits before and after 60 sessions of locomotor training.

Before and after step training, spinal reflexes, neuronal pathways of the spinal cord and clinical outcome measures are being examined in persons with either sensory-motor complete SCI or incomplete SCI. The reflex behaviors, both before and after locomotor training, are compared to that of healthy control subjects under identical conditions of walking.

Testing has been completed in 23 control subjects. During robotic assisted stepping on a moving treadmill, the involved neuronal circuits are engaged, independent of the amount of body weight unloading. Further, during single-legged foot reaching and withdrawal in standing subjects, the soleus H-reflex, the response elicited upon stimulation of the nerve behind the knee, was modulated in a similar pattern to that observed during forward and backward walking. These findings suggest that rhythm of the movement, and not body weight loading, is a key signal to the manifestation of this neural behavior.

Testing has also been completed in two people with SCI who currently receive daily robotic locomotor training. These tests will be repeated again in two months for comparison of pre- and post-training changes of spinal neuronal circuits. Recruitment for additional SCI patients and control subjects continues.

The results from this project will outline the neuronal pathways that play a key role in the recovery of walking after locomotor training in people with a SCI.

Additionally, the researchers are planning to investigate corticospinal plasticity after locomotor training and testing different training intervention paradigms that will be developed based on the relationship between reflex reorganization and clinical outcome measures derived from the current research studies.

**C023691, Margot Meyer-Proschel, Ph.D.**, University of Rochester Medical Center, "Specific Astrocyte Subtypes for SCI Repair Without Allodynia," October 1, 2008 – September 30, 2012; \$1,445,000.

This project is focused on devising a rational approach to identify the optimal cell source and cell population for SCI repair and to characterize the behavioral outcome of the graft cells and the injury site.

The *in vivo* basis for this study is initial experiments transplanting cells derived from embryonic spinal cord glial-restricted precursor cells (GRPs) and induced to differentiate into astrocytes *in vitro* using specific factors. Surprisingly, only astrocytes generated by exposing cultures of purified spinal cord GRPs to bone morphogenetic protein-4 (BMP) promoted extensive regeneration of dorsal column axons in the transected spinal cord, including regeneration of a large proportion of axons through the lesion site and back into normal tissue on the other side of the injury. Extensive regeneration of dorsal column axons in the transected spinal cord is associated with complete functional recovery. In contrast, when the astrocytes were generated using a different signal, or the progenitor population itself was transplanted, graft cells failed to lead to function recovery and produced a neuropathic pain syndrome.

These data clearly indicate that functional recovery can be achieved with a transplant, but it is critical to use the correct cells in the correct context to generate desirable outcomes. This is a significant and important finding for potential translation of the research into human therapeutic approaches.

## **Innovative, Developmental and Exploratory Activities (IDEA) Awards**

**C022060, Ronald Emerson, Ph.D.**, Columbia University Medical Center, “Decoding Motor Intention From Human Microelectrode Grid Data,” April 1, 2007 – March 31, 2010; \$295,160.

Paralyzed patients are limited not only by the impaired ability to move, but also by the inability to manipulate and control their environment by moving. When paralysis is caused by SCI, one approach to restore these capabilities is through systems that allow direct use of internal brain signals encoding intended movements or choices. These brain-machine interfaces (BMIs) may then be able to control devices that supply movement and external control and effectively bypass the devastating functional limitations caused by SCI.

This laboratory gained direct access to internal brain signals using a small array of 96 microelectrodes implanted in the neocortex of patients in whom chronic recordings from electrodes are made as part of surgical treatment for refractory epilepsy. Thus, access was gained to a variety of brain areas, since the site of implantation depends on the part of the brain affected by each patient’s unique epilepsy syndrome.

Researchers have successfully recorded task-related individual neuron activity from human subjects. Activity was found that relates to the context of the task, as well as activity specific to meaningful categories of stimuli, that show promise for development as control signals for BMI devices available from brain areas not usually considered involved with motor control.

Investigations will continue on direct brain signals as selectors for effecting categorical choice and discovering new techniques for using complimentary types of brain signals, unit activity and local field potentials, for this purpose. It is anticipated that neural interface technology now under development will make these brain signals more practically accessible.

Brain-computer interface machines represent an important avenue for improved quality of life for SCI patients. Signals from cortical circuits involved in various cognitive processes provide a richer substrate for categorical information selection than available solely from primary motor processing regions.

**C022064, John Martin, Ph.D.**, Columbia University Medical Center, “Harnessing Corticospinal Activity to Promote Motor Recovery,” April 1, 2007 – March 31, 2010; \$264,085.

Most injuries of the spinal cord are incomplete, with spared connections below the injury site. The Martin laboratory is studying the corticospinal tract, the principal motor pathway, hypothesizing that after SCI, increasing the activity of spared corticospinal tract fibers by electrical stimulation strengthens their connections and improves motor function. Repair of spared corticospinal tract axons was studied in the rat, as well as control of the limb affected by the injury, to promote the motor functions of these spared corticospinal tract axons.

All proposed experiments have been completed. As part of the first aim, it was shown that electrical stimulation of spared corticospinal tract axons in rats caused substantial outgrowth of these axons. It also was demonstrated that this corticospinal tract sprouting resulted in stronger connections with spinal motor circuits. As part of the second aim, it was determined that electrical stimulation of the corticospinal system led to restoration of skilled forelimb movement control. The stimulated group of rats recovered limb control, and the spared

corticospinal tract axons sprouted abundant new spinal cord connections below the injury. By contrast, non-stimulated animals did not recover function, and minimal corticospinal tract sprouting was observed.

Three closely related experiments also were conducted. In the first experiment, it was shown that corticospinal tract stimulation promoted proliferation of oligodendrocyte precursor cells, suggesting that stimulation can promote remyelination after injury. In the second, unexpected functional interactions were discovered among descending motor pathways after injury. This knowledge helps define the rules by which the damaged motor system recovers function. In the third experiment, a novel motor task was developed to study higher-level corticospinal tract control of limb function.

The approach taken provides strong scientific evidence that activity can be harnessed to repair the damaged corticospinal tract and promote skilled motor functions. This strategy can be translated to humans using transcranial magnetic stimulation or transcranial direct-current stimulation.

On the basis of this work, an NIH grant was applied for and obtained to pursue this work further.

**C022065, Dennis Stelzner**, Upstate Medical University, SUNY, "Intrinsic Neuronal Response of Propriospinal Neurons to SCI," April 1, 2007 – March 31, 2010; \$300,000.

Propriospinal (PS) axons interconnect various spinal levels and present a greater potential to regenerate or sprout new connections after SCI than axons from the brain. However, the factors underlying this increased regenerative growth are unknown; many PS neurons die after their axons are cut (axotomy), and regeneration is usually aborted. This project addresses the genetic response of thoracic and cervical PS neurons during the first month after thoracic axotomy/spinal injury.

Many genes in thoracic PS neurons showed an initial upregulation (inflammatory/immune processes; cell death/apoptosis; and neuroprotection/cellular stress, regeneration-related) that returned to near-control levels by the second post-operative week, a time when most other thoracic PS neurons have died. Other researchers have shown that receptors for several growth factors were upregulated, suggesting that these factors would be neuroprotective and sustain regeneration. Cervical PS neurons reacted differently, and a number of genes upregulated in thoracic PS neurons were down-regulated, particularly receptors for growth factors and apoptosis, similar to neurons in the brain after spinal injury/axotomy. The normal baseline expression of many of these genes was higher in cervical than in thoracic PS neurons, possibly related to the differing response of these neurons post-thoracic SCI. The genetic response of a group of genes from cervical and thoracic PS neurons with intact/spared axons passing through thoracic spinal contusion injury was affected similarly, including that of genes related to components of calcium channels and their function, and to spinal injury, suggesting that this type of spinal injury causes secondary intra-axonal pathology. The validation of these genetic findings is ongoing prior to publication, although recently published anatomical findings support these data (Steencken et al., 2009).

The investigators will continue their work to: examine the delivery of identified growth factors that should be neuroprotective and sustain the regeneration of thoracic PS axons; determine whether local inflammation and/or axotomy near the cell body are related to the response of

thoracic PS and long-distance propriospinal tract neurons after thoracic SCI, or if the response is dependent on the class/axonal length of the PS neuron studied; and determine if PS neurons with axons spared by surgical or contusion injury react differently and if spared contused axons can be repaired.

**C022067, Deanna Thompson, Ph.D.**, Rensselaer Polytechnic Institute, “Guided Neuronal and Glial Migration in Electrically Conductive Collagen-Carbon Nanotube Scaffolds,” April 1, 2007 – September 30, 2009; \$212,570.

Following SCI, corresponding tissue damage results in a functional loss at and below the injury site. Although neurons are capable of regeneration, they fail to grow through an injury site and re-establish the integrity of the nervous system for many reasons, including, most significantly: (1) formation of glial scar tissue; (2) failure to overcome the inhibitory signals expressed by the myelin sheath, which insulates and surrounds intact neurons; (3) cell death; and (4) lack of a permissive growth environment, including an appropriate substrate and positive growth factors. Any successful strategy must address all of these issues; however, due to the complexity of a comprehensive approach, most studies have focused on individual cues.

Recent *in vivo* studies have pointed to the potential synergistic effect of combining several strategies into a single intervention; however, it is difficult to determine the relative importance of each component *in vivo*. This work is centered on the hypothesis that guidance cues, such as cellular orientation, growth factors, scaffold orientation, scaffold geometry and electric fields presented to the regenerating axons act synergistically to direct and enhance neurite outgrowth.

The first aim of this project was adaptation of collagen and carbon nanotube scaffolds (col-CNT) to support glial cells. Proposed scaffolds of col-CNT were supportive of neurite outgrowth but did not support glial spreading and growth over a 14-day time period. The scaffold was modified by adding matrix components found in the nervous system (collagen type IV and laminin) via incorporation of Matrigel. The cytotoxicity of single-walled carbon nanotubes (SWCNT) on Schwann cells in cell culture and within the three-dimensional type 1 collagen-Matrigel™ (col-Matrigel) construct has been examined; composites under two percent SWCNT did not exhibit any significant effect on the spinal cord.

The second aim was to investigate glial response to electric field (EF) strength within the col-CNT. An experimental system to monitor the voltage applied to the construct and its temperature in real-time was developed. Prior to applying the varying EF in a more complicated three-dimensional scaffold, an EF in a two-dimensional culture system was employed to examine Schwann cell migration and orientation with respect to the presence and strength of an EF. Results showed that primary neurons have been shown to respond to EFs of 100-200 mV/mm, but primary Schwann cells responded to lower EFs, exhibiting a maximal response at 50 mV/mm.

The third aim was to investigate neuronal outgrowth in response to glial and EF strength in the col-CNT. Neurite outgrowth was assessed on the col-Matrigel composites by placing tissue explants and/or dissociated neurons in the composite material. Schwann cells were placed in a col-Matrigel plug inserted into an acellular col-Matrigel construct. Schwann cells migrated into the construct, indicating their ability to migrate into the material. Neurite outgrowth was greater following stimulation with EF and further increased following co-culture with Schwann

cells. Outgrowth was further increased in an additive manner following co-stimulation with EF and Schwann cells.

In follow-up studies, the effect of scaffold alignment, presence of SWCNT, EF strength and glia (Schwann cells) using dissociated spinal neurons will be examined. The relative contribution of each “cue” will be measured to provide a hierarchy of impact to neurite extension for development of scaffolds for SCI. Several grant applications are pending to continue these research goals.

**C022068, Renato Rozental, Ph.D.**, New York Medical College, “Spontaneous Spreading Depression Enhances Ischemic Spinal Cord Injury,” April 1, 2007 – September 30, 2009; \$300,000.

Spinal cord trauma studies that reprise damage from vehicular or thoraco-abdominal surgeries demonstrate that injury occurs in two stages: the initial, or mechanical, damage at the core and the secondary, or ischemic, damage in the surrounding penumbral region that subsequently leads to delayed cell death. Cells in the penumbral region undergo waves of spreading depression, a massive eccentric wave of stimulation that washes over the adjacent neuronal tissue. This laboratory’s studies in central nervous system tissue show that spreading depression and ischemia-induced delayed neuronal cell death are mediated by cell-to-cell communication via gap junctions. One means to examine gap junctions is through their proteins, connexins (Cx). Because different cell types are coupled by different subtypes of Cx, it is important to determine their differential participation in the process of cell death post-ischemia. The central hypothesis of this work involves how to interfere with the mechanisms that lead to initiation and prolongation of spreading depression waves, thereby changing the outcome and extent of the secondary ischemic lesion that accompanies acute SCI.

These fundamental issues were addressed by combining some well-established techniques with some recent innovative technical advances. This methodology includes: (1) establishing a well-characterized spreading depression model in SCI, allowing application of defined periods of ischemic like-conditions (i.e., hypoxia and hypoglycemia); (2) development of a noninvasive rat model of spinal cord damage centered around Thoracic 10, which closely reprises the damage often seen in vehicular accidents and thoracoabdominal surgery; (3) development and maintenance of mutant mice in which genes encoding Cxs have been reduced or ablated; and (4) access to recently developed pharmacological tools that selectively block subtypes of gap junction channels, specifically, *in vivo* and *ex vivo* proteins that mediate cell-to-cell communication among neurons and among astrocytes.

The findings suggest that blocking initiation of spreading depression is a more effective strategy to confer spinal cord protection than that induced by solely blocking gap junctions. It was found that microglia can be activated by spreading depression waves and that, vice versa, activated microglia contribute to spreading depression through upregulation of Cx43 in astrocytes. The researchers succeeded in identifying upregulation of specific activating factors, cytokines/chemokines, that precede the advent of activated microglia and facilitate development and expansion of the lesion and neuronal death. Formation of the initial punctuate lesion requires a minimum of three to four spreading depression episodes within the first two hours of injury onset, and it is from these areas bordering the lesion that spreading depressions are generated. As the spreading depressions reverberate, they activate microglia in the epicenter of the lesion at 24 hours post injury. As subsequent

spreading depressions are generated, the primary punctuate lesion enlarges and expands into the penumbral region.

Future research will investigate the effects of depletion or blockade of microglia activation post injury in the spinal cord, in an attempt to prevent expansion of the lesion. If successful, these studies may lead to a novel treatment for spinal cord ischemic insult.

**C023679, Avraham Dilmanian, Ph.D.**, Stony Brook University, SUNY, "Promoting Recovery of Spinal Cord Injury Repair With Microbeams," October 1, 2008 – September 30, 2010; \$343,856.

Injuries to the spinal cord can kill a large portion of all cells involved, including neurons, endothelial cells that make up capillary blood vessels and glial cells. A large number of immune cells enter the tissue from the damaged capillary blood vessels and can impede recovery instead of enhancing it. The hypothesis of this research is that dose-fractionated, angle-varied microbeam irradiation of a contusion-injured rat spinal cord will help the cord regain its function by promoting remyelination and reducing the population of unwanted immune cells.

In this study, contusion-injured spinal cords in rats were irradiated with arrays of parallel, very thin planes of X-rays called microbeams, administered to the injured spinal cord over five days from five different angles (i.e., five-dose fractions). The results indicated a slight improvement in the functional recovery of the contusion-injured rat spinal cord compared to that of the unirradiated rats, measured by Basso, Beattie and Bresnahan (BBB) scores (a scoring method with a 0-21 scale) over 100 days following injury.

Follow-up studies using a different irradiation pattern on-center in a single exposure and perpendicular to the rat's back, were also successful. The result was a statistically significant improvement in the function of the rats' hind legs for a period of about 17 to 70 days after the injury, as evident from measured BBB scores of the rats. It is assumed that the observed positive results were caused mostly by reduction in the number of unwanted immune cells at the early stages after injury through a direct hit by microbeams. However, the superiority of the scores for the irradiated rats gradually diminished with time. It appears that the detrimental effects of the immune system response overshadowed any positive effects of the glial system.

As a result, additional experiments are being conducted that concentrate on the effects of the immune response, timing the irradiation to coincide with peaks in the populations of certain types of immune cells.

If proved successful, these methods could have a great impact on treatment of SCI and brain trauma patients: the treatment would be extremely easy, fast and simple. Treating in a single session would be much easier to implement than the dose-fractionated radiation techniques used in cancer therapy today.

**C023680, Jun Yan, Ph.D.**, Regenerative Research Foundation, “Human Neural Stem Cell Cultures From Adult Spinal Cord,” October 1, 2008 – September 30, 2010; \$360,000.

Neural stem cells can self-renew and generate all three major cell types of the CNS: neurons, astrocytes and oligodendrocytes. Neural precursor cells are also capable of self-renewing, but are restricted to producing only certain neural cell types. Neural stem cells and neural precursor cells hold great potential as cell sources for treating SCIs with transplantation. Researchers in this project have been working on culturing neural stem cells and neural precursor cells from donor adult human spinal cord tissue and further generating neurons, including motor neurons and oligodendrocytes from cultured cells.

This laboratory has optimized various procedures for tissue dissociation, live cell isolation and cell culture conditions. However, the researchers have been unable to expand human spinal cord cells using the two traditional methods of culturing neural stem cells or neural precursor cells, e.g., as adherent (cells attached to a growth surface) and neurosphere (floating cell aggregates) cultures. Various means to promote cell growth have been attempted, including use of additional mitogens/growth factors, different culture media and overexpression of transcription factors that promote neural stem cell proliferation. None of these measures resulted in sustained cell growth.

However, when human spinal tissues were cultured as thin slices and small tissue chunks without dissociation of the tissue, sustained growth was observed, as evidenced by enlargement of the tissue, more dividing cells and higher cell density. Immunofluorescence staining with antibodies that recognize specific types of cells indicated that most of the newly generated cells were neural-restricted precursors, a major type of neural precursor cells that generate only neurons but no glial cells. Retaining relative tissue integrity that facilitates cell-to-cell support and interactions may have played a major role in enhanced cellular survival and growth of these cultures.

This is the first time that neural stem cells and neural precursor cells have been derived from human spinal tissue using cultured tissue slices, mostly as an *in vitro* model for SCI instead of long-term cell cultures. This achievement generated suitable cells for the second objective of this proposed work – to derive motor neurons. Successful completion of this project will make human spinal cord tissue from organ donors a new and rich cell source of transplantation therapies for SCIs and other conditions.

**C023681, Joel Levine, Ph.D.**, Stony Brook University, SUNY, “Functions of Atypical Protein Kinase C in Axon Regeneration,” October 1, 2008 – September 30, 2011; \$359,973.

When the spinal cord is injured, the environment of the spinal cord contains numerous molecules that inhibit axon regrowth. Prominent among these are a class of extracellular molecules known as chondroitin sulfate proteoglycans (CSPGs). These molecules are potent inhibitors of axon growth but how they act to compromise the growth machinery is unknown. The goal of this project has been to determine whether the par complex plays a role in axon growth inhibition by extracellular molecules.

The par complex comprises at least three proteins – atypical protein kinase C (aPKC), par3 and par6 – that regulate many types of motile events in all cells. Because of its central role in cell motility, the par complex is likely to become an important final target for extracellular molecules that regulate axon regeneration.

The general approach was to treat neuronal cells with several molecules that inhibit axon growth and examine the functions of components of the par complex using biochemical techniques. Axon growth also was monitored *in vitro* from the treated cells.

The investigators have made considerable progress in defining a role for the par complex and associated proteins in the axonal response to CSPGs. Results of the studies suggest that aPKC may be an important responder to extracellular signals that inhibit axon regeneration after SCI. The findings emphasize the possibility that microtubules might be a final target for growth-inhibitory molecules. Thus, these studies have identified new and novel mechanisms whereby glial-derived molecules may prevent successful axon regeneration after SCI.

**C023682, John Chapin, Ph.D.**, Downstate Medical Center, SUNY, “Neural Prosthesis to Restore Touch Sensation in Spinal Cord Injury,” October 1, 2008 – September 30, 2010; \$360,000.

Humans and animals rely on sensory feedback to act in their environment. Neurological disorders such as SCI can disrupt the link between brain and peripheral limbs, leading to usually unrecoverable loss of sensorimotor functions. Recent advances in BMI technology have shown that it is possible to restore basic motor functions by translating brain activity directly into motor commands enacted by artificial actuators. However, somatosensory feedback has not yet been incorporated into BMI, although it would be essential for optimal BMI control. This laboratory is investigating the feasibility of substituting somatosensory feedback with electrical stimulation in the central somatosensory pathway.

This project addresses the following topics: (1) somatosensory coding of touch and/or proprioceptive stimulus, and brain microstimulation-evoked cortical responses; (2) comparison of cortical responses evoked by natural touch and thalamic microstimulation; and (3) optimizing the parameters of thalamic stimulation to emulate natural touch.

The first aim of this project is to determine how accurately thalamic microstimulation can emulate natural touch. Researchers have demonstrated that appropriate thalamic microstimulation can produce neural response patterns (in the somatosensory cortex) that are remarkably similar to those produced by natural touch. A manuscript reporting these results has been completed and will be submitted to the *Journal of Neuroscience*. The second aim is to train monkeys to discriminate somatic stimuli delivered either from touching the skin or from microstimulation of the somatotopically equivalent region of the ventral posterior thalamus. The software code to train the monkeys has been developed, and two monkeys have learned to move a mechanical arm using their right arm/hand according to instructions on the screen just below their face. Tactile stimulation will be introduced during the instruction period. With the monkeys' behavioral training at full schedule, these animals are expected to be implanted in the very near future.

Investigators expect that the monkeys can be fully trained to perform the appropriate discrimination tasks. Microelectrode arrays will be implanted in the somatosensory thalamus and cortex. Once the monkeys learn the psychophysical task successfully, electrodes will be chronically implanted in the somatosensory cortex and ventral posterior thalamus. Microstimulation of ventral posterior thalamus will be performed. The monkeys then will be tested for the ability to differentiate the thalamic stimulus from the natural touch. This laboratory will continue to analyze the data collected and to formulate new computational

models of the sensorimotor control system. If the feasibility of substituting natural touch with thalamic microstimulation is demonstrated successfully, this microstimulation technique can be expected to improve the quality of life of patients suffering from SCI.

**C023683, William Collins, Ph.D.**, Stony Brook University, SUNY, “Bladder-Sphincter Dyssynergia: Role of Intrinsic Motoneuron Properties,” October 1, 2008 – September 30, 2010; \$358,552.

Bladder-sphincter dyssynergia (failure of muscle coordination) frequently is a consequence of injury to the spinal cord that interrupts neuronal connections between the brainstem and the lumbosacral spinal cord. The dyssynergia is characterized by hyperactivity of the external urethral sphincter (EUS), so that the EUS fails to relax during bladder contraction, leading to incomplete voiding and urine retention. While bladder-sphincter dyssynergia is a direct result of loss of brainstem coordination in spinal bladder and EUS reflexes, its underlying mechanisms have not been fully elucidated. In particular, little consideration has been accorded to the possible role of injury-induced changes in the intrinsic electrical properties of EUS motoneurons.

The goal of this project is to develop a new model of bladder-sphincter dyssynergia in the rat and to identify spinal cord transection-induced changes in the intrinsic electrical properties of EUS motoneurons that may contribute to bladder-sphincter dyssynergia.

During the first year of the project, work has focused on establishing basic experimental models in the laboratory, and two studies characterizing bladder-sphincter reflexes in spinally intact and transected adult rats have been completed. Experiments have begun involving *in vivo* intracellular recording from EUS motoneurons. Future research will focus on: 1) integrating *in vivo* intracellular recording from EUS motoneurons and continuous flow urodynamic recording of bladder-sphincter reflexes both in intact and transected rats; and 2) quantifying changes in EUS motoneuron electrical properties following spinal cord transection that could be responsible for bladder-sphincter dyssynergia.

Identification of an EUS motoneuron-based mechanism should provide a new model for understanding the etiology of bladder-sphincter dyssynergia and for development of effective new therapies.

**C023684, Zaghoul Ahmed, Ph.D.**, College of Staten Island, CUNY, “Acrobatic Exercises and Spinal Stimulation After Spinal Cord Injury,” October 1, 2008 – September 30, 2010; \$309,655.

Pathological changes in the peripheral nerves and muscles following SCI have been reported in several human and animal studies. However, the mechanisms for these changes are not well understood. The focus of this project is to identify mechanisms mediating these negative changes in peripheral nerves and muscles.

Excessive release of glutamate, a major excitatory neurotransmitter in the spinal cord, following injury contributes to excitotoxicity and secondary lesions. This laboratory has investigated the influence of different types of stimuli on the release of glutamate from segments of the spinal cord.

Using biochemical, electrophysiological and immunostaining methods, the research established that SCI induces negative alterations in expression of sodium channels, myelin and muscle contractility.

Overall, these results indicate that severe sciatic nerve abnormalities develop following SCI. Therefore, more efforts should be directed toward finding mechanisms for maintaining or improving the condition of peripheral nerves in subjects with SCI. In addition, knowledge of the magnitude and time course of glutamate release should help identify windows for interventions to prevent neural damage by neurotoxicity, or to modify and harness this release to improve functional movement following SCI.

Next, the effect of the treatment strategy on reversing and/or preventing these changes will be investigated. Studies also will be continued to determine the magnitude and dynamics of glutamate release after mechanical, electrical and magnetic stimulation.

**C023685, Aiko Thompson, Ph.D.**, Helen Hayes Hospital, “EMG/EEG Training to Improve Motor Function After Spinal Cord Injury,” October 1, 2008 – September 30, 2010; \$337,875.

With the development of regeneration therapies, rehabilitation for functional recovery is becoming increasingly important for re-establishing an active, productive, fulfilling life in those with SCI. To maximize functional recovery after SCI, continuing development of new therapeutic approaches beyond conventional rehabilitation techniques is extremely important. The goal of this project is to evaluate electromyogram/electroencephalogram training as a new therapeutic approach and to investigate whether the successful muscle response training leads to improvement of gait in people with SCI.

Individuals recovering from SCI are often left with remaining chronic movement disabilities, such as spasticity and weak voluntary muscle control, even after completing conventional therapies. These problems likely originate from a combination of changes in muscle properties and spinal reflexes and disturbed brain-spinal cord connections.

Through training, individuals can learn to produce specific patterns of neural activity to control muscles in response to a stimulus or brain-wave activity. Investigators have found that the muscle response training to train a spinal reflex response induces lasting changes in reflex pathways and movement disabilities due to SCI may be alleviated. After several years of successful animal research, a muscle response training protocol has been developed for humans.

This project includes two muscle response training studies: spinal reflex training and brain stimulation training. To date, both training studies have shown that most of the subjects with SCI are able to learn to control the muscle response. The subjects who successfully completed the training have shown various extents of improvement in speed, step control and muscle activation patterns during walking. Also, the investigation of brain-wave activity during training sessions has indicated that certain patterns of brain activity may be associated with successful muscle response training.

Given the laboratory’s promising preliminary results, the researchers plan to increase the number of study participants and expand the current project by treating other movement problems, such as arm flexor spasticity and weak wrist/hand control, as repeatedly requested by many study participants.

With the success of this project, a five-year research grant from the NIH has been obtained, which will help researchers further examine the therapeutic effects of their training approach in improving gait after SCI. Multi-center trials for evaluating the therapeutic effects of this approach in a larger scale and training of upperlimb for improving hand/arm functions are planned for the future.

**C023686, Jessica Treisman, Ph.D.**, New York University School of Medicine, “Developing *Drosophila* as a System to Study Axon Regeneration,” October 1, 2008 – September 30, 2010; \$354,604.

SCI can cause devastating disabilities. An increased understanding of the molecular mechanisms of axonal regeneration would open new avenues for treatment. The goal of this project is to identify novel factors that promote or block axonal regeneration.

This laboratory is developing genetic methods, using the model organism *Drosophila melanogaster* to damage axons reproducibly, in order to examine whether they are able to regenerate in otherwise normal animals. Further, researchers are studying the expression of molecules known to augment or retard axonal regeneration in vertebrates and are determining whether they produce similar effects in *Drosophila*. A genetic screen will be performed to identify new molecules that alter the efficiency of axonal regeneration.

Efforts to date have focused on developing methods for studying axonal regeneration in *Drosophila*. Transgenic flies have been generated; these flies are capable of expressing fusion proteins that link the cell death protein with two synaptic proteins transported along axons toward synapses. In cell culture, it was shown that the cell death protein is active in these chimeric proteins and kills the cells that produce it. *In vivo*, expression of these fusion proteins in all cells destroys the whole animal, and expression in one specific class of adult photoreceptors results in loss of the axon terminals in these neurons.

Researchers are establishing the best conditions for specifically damaging photoreceptor axons without killing the cell bodies, by testing different time periods of conditional transgenic protein expression and will investigate time periods for axon regrowth. If regrowth is not observed, this laboratory will ascertain whether regrowth can be induced by activation of the Jun kinase pathway, which has been shown to stimulate regeneration in other systems. Success in this component of the project would establish *Drosophila* as a useful model for regeneration studies.

## Mentored Scientist Development Awards

**C022046, Donna Osterhout, Ph.D.**, Upstate Medical University, SUNY, “Neural Effects of Release of cABC and GDNF Caudal to SCI,” April 1, 2007 – March 31, 2010; \$285,677.

For those with a traumatic SCI, the ability to restore nerve connections is highly dependent on survival and regeneration of neurons in the spinal cord. The goals of this study are to enhance neuroprotection, minimizing the damage resulting from the injury; and to promote neuroplasticity, stimulating neurons spared by the injury to sprout, make new connections and assume some of the functions of damaged axons.

A number of studies identify neurotrophins, in particular glial-derived neurotrophic factor (GDNF), as an agent that enhances neuronal survival and promotes sprouting of propriospinal projections after axotomy. This laboratory has developed a nanosphere drug-delivery system to treat SCI and used it successfully to deliver the enzyme chondroitinase ABC (cABC) to the lesioned cord. The system degrades the inhibitory proteoglycans in the glial scar more effectively than a simple injection of the enzyme, enhancing axonal sprouting in and around the lesion site. In this study, two approaches are combined, using nanospheres that release neurotrophins and cABC to promote survival of the spared neurons and stimulate sprouting from their terminal arbors. Specifically, this study is designed to determine whether survival and sprouting of propriospinal neurons post SCI can be augmented by injections of nanospheres that release GDNF and cABC and to test their effect on functional recovery in a rat model of SCI.

At present, a new formulation of GDNF nanospheres that can be released for longer time periods is undergoing testing, and the effects of these agents on remyelination of surviving axons is being characterized.

This laboratory will continue *in vivo* studies with these nanospheres, looking at neuronal survival and sprouting after treatment with GDNF and cABC nanospheres. It is believed that an increase in neuronal survival and regenerative sprouting will be seen with this treatment. Moreover, the studies have demonstrated that these agents may enhance remyelination. The data suggest that these treatments will have a significant impact on functional recovery after injury.

**C022048, Joseph Francis, Ph.D.**, Downstate Medical Center, SUNY, “Neural Control of Force in a Brain-Machine Interface,” April 1, 2007 – March 31, 2010; \$300,000.

This laboratory is researching the BMI, using equipment such as a robotic prosthesis that will allow an individual to move a robotic arm. Recently, it has been shown that this is not only possible, but that the limits of such technologies are wide open. To date, no BMI has allowed its user to control how much force is output – a capacity clearly needed in everyday situations. This grant has supported such work, and the results and conclusions are below.

The laboratory has implemented a real-time BMI using both kinematic and dynamic variables. The world’s first BMI has been built that controls the forces the user intends to output. Monkeys made reaching movements while wearing an exoskeletal robotic system. These animals were implanted with arrays of microelectrodes to record neural activity from the brain regions involved in motor control. They worked against a range of dynamic environments to

allow separation of neural information related to different force-related information, such as joint torques and forces at the hand.

To date, four monkeys have been trained to make the above-described reaching movements, and two recently have been implanted with 300 electrodes in several areas of the sensorimotor cortex. Researchers have obtained a great deal of data from implanted animals. The animals move a visual hand-feedback cursor that indicates where their hand is in a virtual world, and the size of this feedback cursor changes as a function of the virtual object's "weight." It is being determined which portions of the cortex code for the various visual, somatosensory and motor components of such reaching/transporting tasks.

This laboratory's aims in this project have now been accomplished by closing the loop on the BMI with force control, as experiments already have been conducted allowing monkeys to control the visual cursor while working against various dynamic environments. Data from these experiments are being analyzed.

In the next year, researchers will continue to run the force-related BMI to determine its ability to generalize from one dynamic environment to others. New computational models of the sensorimotor control system will be formulated, results published and new directions pursued, including developing a BMI that learns along with the user in a cooperative manner.

**C023688, Jiyun Kim, Ph.D.**, NYU School of Medicine, "CXCR6 and Central Nervous System Injury," October 1, 2008 – September 30, 2011; \$648,000.

Direct visualization of a SCI by intravital imaging in rodent models can illuminate the critical stages of inflammatory response to the injury by studying labeled cell populations and their behavior. This project addresses the critical need to develop an animal model and an intravital imaging system whereby specific components and candidate molecules can be tested for therapeutic outcome and for the actual inflammatory parameters during visualization of the process. The candidate molecules to be examined first are a chemokine receptor expressed in some activated immune cells in CNS injury, CXCR6, and its binding target CXCL16. Concurrently, the role of another molecule in CNS injury, myristoylated alanine-rich C kinase substrate (MARCKS), is also being studied.

Intravital imaging was assessed using fluorescently labeled cell populations of interest for stable time-lapse imaging. The investigators have found that effector immune cells amplify within the central nervous tissue by interaction with antigen-presenting dendritic cells, which also invade the covering of the brain during inflammation in an antigen-dependent manner.

It was found that CXCR6 and CXCL16 play a role only in gray matter injury in a chronic inflammatory setting but not in an acute setting of a healthy animal. Investigators are now pursuing this study in a different model of experimental autoimmune encephalitis – a relapsing, remitting form.

Many key immunological molecules remain to be identified in acute and chronic phases of inflammation accompanying SCI, as each minute counts for salvaging neuronal function. The role of MARCKS in microglial injury response is being assessed. More specific experiments will be carried out for examining MARCKS, including generation of a transgenic mouse model that expresses a reporter fusion protein in the microglia. These mice will help in probing for direct immunological dynamics in these molecules by imaging.

**C023926, Takahiro Takano, Ph.D.**, University of Rochester, “Failure of the Microvasculature Following Spinal Cord Injury,” October 1, 2008 – September 30, 2011; \$648,000.

Local blood perfusion, the process of nutritive delivery of arterial blood to a capillary bed in the biological tissue, is often compromised in the peri-traumatic areas following SCI and decreased delivery of oxygen, resulting in an expansion of tissue injury. Tissue injury in other organs leads to loss of glycocalyx, a carbohydrate coating of vessel endothelial cells. Loss of glycocalyx results in secondary injury by reducing blood circulation in areas surrounding the traumatic lesion. In this study, the consequences of loss of glycocalyx in the SCI will be defined.

Imaging microcirculation and microglial activation within and surrounding the SCI in intact animals using a two-photon microscope has begun. This imaging is more challenging compared to live brain imaging because of significant movement of the target field resulting from breathing and heartbeat and limited visibility through the white matter region of the spinal cord. It was possible to capture the leakage of small molecules from blood vessels in intact tissue after injury, a novel observation. This leakage could likely lead to very serious consequences, as nervous tissue must always be protected from exposures to blood plasma contents that are toxic to neurons.

Thus far, researchers have successfully measured the glycocalyx layer of capillaries in spinal cord tissue before and after SCI. The measurements showed a decrease in the thickness of the layer, along with reduction of flow, showing that the loss of the glycocalyx layer was an early event after the injury, preceding the onset of the development of secondary injury. At 24 hours, peri-traumatic regions were virtually devoid of fast-flowing capillaries. Therefore, soon after the initial SCI, the reduction of both the glycocalyx layer and capillary flow rate occur. Now, the tissue oxygen level supplied by a single capillary is being measured, to confirm that the reduction of capillary blood flow leads to the shortage of oxygen supply.

Imaging quality will continue to be improved to obtain better visual documentation of microscopic activities and changes in the injured spinal cord that lead to expansion of injury after the initial injury. Next, researchers will proceed to imaging of local blood flow and congestion by glycocalyx aggregates in spinal cord-injured animals.

### **Postdoctoral Fellowship Awards**

**C022050, Ramiro Almeida, Ph.D. (initially Ulrich Hengst, Ph.D.)**, Weill Medical College of Cornell University, “Regulation of RhoA mRNA in Spinal Cord Injury,” April 1, 2007 – March 31, 2010; \$120,000.

The enzyme RhoA regulates the axonal cytoskeleton and is thought to contribute to the inability of axons to grow after SCI. Inhibitors of RhoA or its principal effector, Rho-activated kinase, are capable of enhancing axonal growth and sprouting after various types of SCI. Further, increasing evidence has linked synthesis of the protein actin in growth cones to axonal growth. Thus, studies that enhance understanding of the mechanisms that regulate RhoA activity in the injured axon, as well as the actin cytoskeleton, potentially could lead to new strategies in SCI therapy.

The major goal of this project is to identify mechanisms by which translation of actin and RhoA is regulated in injured axons. This laboratory is characterizing specific factors that regulate the synthesis of actin and RhoA. In the case of RhoA, researchers are evaluating whether RhoA mRNA is present in injured axons and whether its translation is induced by components of myelin.

Studies performed both in cultured neurons and in an *in vivo* model of axonal injury support the concept that axonal injury is associated with increased protein translation within the regenerating axon. Data, both functional and microscopic, also have been acquired, that bolster the hypothesis that RhoA and beta-actin messenger RNA, or mRNA, are translated within regenerating axons and in axons forming synapses. These studies may uncover new strategies for reducing RhoA signaling after SCI and identify functions of actin that may be relevant for reestablishing synaptic connections following injury.

**C022051, Igor Smirnov, D.V.M., (initially Lara DeRuisseau, Ph.D.)** Upstate Medical University, SUNY, "Ventral Root Stimulation to Enhance *cauda equina* Repair," April 1, 2007 – March 31, 2010; \$119,950.

Nerves that have been crushed or cut do not normally grow back to their original target, muscle or skin, without some help. This usually takes the form of surgical treatment to line the nerves back up again, with the hope that nerves will regrow, or regenerate, and restore function. The usual rate that nerve fibers regenerate after an injury is about 1 mm per day, so recovery times can take many months, depending on where the nerve injury took place. At the present time, the only treatment for patients who break their back causing injury to the *cauda equina*, the nerves at the base of the spinal cord, is spine fusion. In contrast, repair to the nerves making up the *cauda equina* is never attempted, because it is thought to be a waste of time and effort. Researchers are establishing whether repair of *cauda equina* can be done safely and effectively.

The investigators showed that individual nerve roots making up the *cauda equina* could be identified based on their response to electrical stimulation, which had never been done before in the rat. They then evaluated how quickly nerve roots degenerated after being cut close to the spinal cord, information that is important should the project move to clinical trials. They learned that as long as nerve root stimulation happens within two days of injury, the stimulation frequently elicited responses from muscles in the tail. Conversely, they learned that waiting three days before stimulation was applied resulted in a complete loss of responses. The results from electrical testing were confirmed by labeling nerve fibers and looking for signs of degeneration under the microscope.

Further, now that the injury model has been developed, individual nerve roots supplying the tail were injured and are being studied for signs of recovery, either by natural regeneration alone, or using a growth channel, nerve growth factors, supporting cells and anti-scar factors. The most successful results from these studies will then be paired with electrical stimulation in an effort to further improve nerve regeneration.

The general approach thus far continues to show promise as a repair strategy in humans.

**C023687, Jin-Wu Tsai, Ph.D.**, New York University School of Medicine, “Removing Microglia From Glial Scar Following Spinal Cord Injury,” October 1, 2008 – September 30, 2010; \$125,280.

The failure of axonal regeneration in the CNS is thought to be related to the scar that forms at the injury site. Accumulation of microglial cells in the SCI is an important component of glial scar which prevents axonal regeneration. To better understand the processes of scar formation and axonal regeneration, the investigators used two-photon microscopy to image microglia accumulation and neurite regeneration over various time periods in both the injured spinal cord and the cerebral cortex of living mice. Results indicate that microglia accumulated rapidly and remained at the site of injury over at least 10 days. During this period, no obvious signs of regeneration of axonal and dendritic branches were observed surrounding the site of injury.

To examine whether the size of injury affects the regeneration processes, investigators developed a two-photon line scan method to injure individual axons and dendrites in the living spinal cord and cerebral cortex. The researchers also developed a new stabilization method which greatly reduces the effects of breathing movements on the stability of the spinal cord, allowing high-resolution imaging of GFP-labeled microglia and interferon-gamma-producing Th1 cells over time. As a result, they learned that in addition to microglia, IFN-gamma producing Th1 cells are also recruited to the site of injury over time, suggesting that peripheral T cells are likely an important component of glial scar and may play a role in axonal regeneration.

They found that regardless of the size of the injury, injured axons and dendrites generally fail to regenerate over a period of days in the CNS. These results reveal that persistent microglia accumulation and failure of neurite regeneration are common features in the injured spinal cord and cerebral cortex.

Additionally, the effect of an ATP gradient to induce microglia migration away from the glial scar was also tested. The study showed that while microglial processes could be induced to move away from the site of injury over hours, the accumulation of microglia at the site of injury over days to weeks could not be prevented. These results suggest that permanent removal of microglia from the scar would require other means, such as the use of mutant mice in which microglia migration mechanisms are disrupted.

The researchers explored the use of the CX3CR1-CreERT2/DTR mice to ablate microglia from the site of injury to determine if axon regeneration would be enhanced. Preliminary results show that in CX3CR1-CreERT2 mice, most of the microglia in the cerebral cortex were rapidly deleted.

Future plans include characterizing the ablation of microglia in the spinal cord using Rosa26-DTR mice crossed with CX3CR1-CreERT2/YFP-H mice and determining scar formation and axonal regeneration with or without microglia ablation to gain important insights into microglia function in SCI.

## Program Projects Award

**C023832, Samie Jaffrey, Ph.D.**, Weill Medical College of Cornell University, “Synthesis and Evaluation of NAD-Augmenting Agents for Spinal Cord Injury,” January 1, 2009 – December 31, 2013; \$2,409,665.

The development of effective therapies for spinal cord injury represents a major goal in medical research. SCI is associated with both a neurodegenerative pathology, as well as an axon degeneration pathology. After injury, the distal part of the axon degenerates. Additionally, many of the neurons themselves undergo cell death. Preventing both of these types of acute injury mechanisms could substantially improve the prognosis for people who have undergone SCI.

An exciting new development is the identification of the coenzyme nicotinamide adenine dinucleotide (NAD) as a regulator of both these processes. NAD is a naturally occurring cofactor found in the body, and therefore presents an exciting avenue for the treatment of SCI. In particular, treatment of cells with NAD reduces their susceptibility to a wide variety of cytotoxic insults. Additionally, treatment of axons with NAD substantially delays axonal degeneration. Researchers are studying how NAD levels can be augmented in neurons and the molecular pathways that mediate the protective effects of NAD.

To address these issues, the investigators are developing a series of molecules that increase intracellular NAD levels. Highly efficient synthetic protocols to produce these NAD augmenting agents in quantities sufficient for biological experimentation have been developed. The compounds have been tested in different types of neurons. Several of these compounds are capable of increasing intracellular NAD levels and protecting them from models of injury that mimic those seen in SCI. Additionally, new intracellular mechanisms that explain the mechanism of action of NAD have been identified.

Together, these experiments represent significant progress towards the development of NAD-related therapeutics for the treatment of SCI.

## Richter Center of Research Excellence Award

**C019772, Rajiv R. Ratan, M.D., Ph.D.**, Winifred Masterson Burke Medical Research Institute, “A Novel Multimodality Approach to Treating Spinal Cord Injury,” May 1, 2004 – April 30, 2010; \$14,996,020.

The Richter Center of Research Excellence (CORE) made significant progress in discovering new therapies that may ultimately comprise multi-modality treatments for acute and chronic SCI. The ultimate goal of the program is to combine drug therapy, robotics enhanced rehabilitation and cellular transplantation methods to improve the quality of life of individuals with SCI.

Project 1 consists of high throughput screening of 2000 compounds from a library of FDA approved drugs and nutraceuticals. This project has been significantly successful by yielding an impressive 30 possible drug candidates that enable axon growth on inhibitory substrates. Of these, the most promising, L-DOPA and lithium, are well known to penetrate the blood-brain barrier and therefore constitute excellent translational candidates. The CORE drug discovery effort has also resulted in the development of novel screening methods for the

discovery of small molecule regulators of factors that respond to changes in oxygen in the cellular environment.

Research on inhibitory factors that inhibit neuronal growth, as outlined in Project 2, has provided evidence that mechanisms of neuronal growth inhibition and attenuation of synaptic plasticity are related. Thus, the same inhibitors and their receptors that are thought to play a role in impeding regeneration may coordinate structural and functional neuronal plasticity in CNS health and disease. This means that understanding their role in the normal CNS is essential in order to design therapeutic approaches.

The Goal of Project 3 was to define the precise cells to transplant to improve functional recovery after SCI. CORE researchers (also see #C023691, above) discovered that transplantation of astrocytes generated by exposure of embryonic GRP cells of bone morphogenetic protein-4, known as glial-restricted precursor derived astrocytes BMP, or GDAs<sup>BMP</sup>, promotes extensive recovery from SCI. In addition, transplantation of GDAs<sup>BMP</sup> generated *in vitro* from GRP cells can be replicated with human cells. As with rat-derived cells, the human cells also have to be pre-differentiated into this specific astrocyte population in order to optimize benefit. CORE researchers also developed a panel of markers that allow useful astrocytes that provide the quality control needed for further development of this promising therapeutic strategy and that can be distinguished from a different type of astrocytes that do not promote recovery.

Project 4 focused on the development and use of interactive robot technology to improve therapeutic outcomes in people with SCI. A tremendous amount of work went into engineering and perfecting devices to adequately and effectively accomplish this task. Six patients with SCI at cervical vertebrae C4-C6 underwent robotic training of each shoulder and elbow in 36 sessions, 3 times per week. Standard clinical measurements were obtained prior to training, at the midpoint and at discharge. All patients demonstrated improved motor function of the shoulder and elbow, as demonstrated by improved Fugl Meyer and Motor Power scores. These advances indicate that robotic therapy is an effective and viable alternative to standard physical therapy and can be used in conjunction to increase the quality of life for patients with SCI.

## **VI. CONCLUSION**

The Board urges continued support so this very successful SCI research program can continue to develop treatments, alleviate pain associated with SCI, restore function and ultimately find a cure for SCI.

**Appendix I**  
**Laws of New York State**

**Public Health Law, Title IV, § 250. Spinal Cord Injury Research Board.**

1. A spinal cord injury research board is hereby created within the department for the purpose of administering spinal cord injury research projects and administering the spinal cord injury research trust fund created pursuant to section ninety-nine-f of the state finance law. The purpose of research projects administered by the board shall be neurological research towards a cure for such injuries and their effects. The members of the spinal cord injury research board shall include but not be limited to representatives of the following fields: neuroscience, neurology, neuro-surgery, neuro-pharmacology, and spinal cord rehabilitative medicine. The board shall be composed of thirteen members, seven of whom shall be appointed by the governor, two of whom shall be appointed by the temporary president of the senate, two of whom shall be appointed by the speaker of the assembly, one of whom shall be appointed by the minority leader of the senate, and one of whom shall be appointed by the minority leader of the assembly.
2. Board members shall be reimbursed for ordinary travel expenses, including meals and lodging, incurred in the performance of duties pursuant to section two hundred fifty-one of this title.
3. The terms of board members shall be four years commencing January first, nineteen hundred ninety-nine.
4. At the end of a term, a member shall continue to serve until a successor is appointed. A member who is appointed after a term has begun shall serve the rest of the term and until a successor is appointed. A member who serves two consecutive full four year terms shall not be eligible for reappointment for four years after completion of those terms.
5. A majority of the full authorized membership of the board shall constitute a quorum.
6. One member of the board shall be chosen by the governor to serve as chairperson.
7. Meetings of the board shall be held at least twice a year but may be held more frequently as deemed necessary, subject to call by the chairman or by request of a majority of the board members. Board meetings shall concern, among other things, policy matters relating to spinal cord injury research projects and programs, research progress reports, and other matters necessary to carry out the intent of this title.
8. Members of the board shall be indemnified pursuant to section seventeen of the public officers law.

#### **Title IV, § 251. Powers and Duties.**

The spinal cord injury research board created pursuant to section two hundred fifty of this title shall:

1. Formulate policies and procedures necessary to carry out the provisions of this title;
2. Solicit, receive, and review applications from public and private agencies and organizations and qualified research institutions for grants from the spinal cord injury research trust fund, created pursuant to section ninety-nine-f of the state finance law, to conduct research programs which focus on the treatment and cure of spinal cord injury. The board shall make recommendations to the commissioner, and the commissioner shall, in his or her discretion, grant approval of applications for grants from those applications recommended by the board.
3. Ensure that state funds, appropriated for spinal cord injury research are not diverted to any other use; and
4. Provide the governor and the legislature an annual report by January thirty-first of each year succeeding the year in which this title shall take effect setting forth the status of funds appropriated for spinal cord injury research and the progress of the Board in terms of the results of its spinal cord injury research efforts.

#### **Chapter 338, Laws of 1998, as Amended by Chapter 612, Laws of 1999\*\***

Section 1. Section 4 of Chapter 338 of the laws of 1998, amending the public health law, the public officers law and the state finance law, relating to establishing a spinal cord injury research board, is amended to read as follows:

**§ 4.** Notwithstanding any inconsistent provisions of law to the contrary, effective April 1, 1999, an amount not to exceed \$8,500,000 shall be annually transferred from the general fund out of the mandatory surcharges collected pursuant to subdivision 1 of section 1809 of the vehicle and traffic law to the spinal cord injury research trust fund held by the state comptroller pursuant to section 99-f of the state finance law which monies shall then be deposited to the credit of the spinal cord injury research trust fund pursuant to section 99-f of the state finance law. Each such payment shall be accompanied by a true and complete report in such form and detail as the comptroller shall prescribe. Nothing contained in this section shall be construed to authorize the transfer to the spinal cord injury research trust fund of any monies collected under section 1809 of the vehicle and traffic law that are otherwise authorized to be deposited to the credit of the criminal justice improvement account established pursuant to section 97-bb of the state finance law.

\*\* This section was not codified to law; however, the State Finance Law, as amended by Chapter 612 of the Laws of 1999, currently reads as follows:

**State Finance Law, Article 6**

**§ 99-f. Spinal cord injury research trust fund.**

1. There is hereby established in the joint custody of the state comptroller and the commissioner of taxation and finance a special revenue fund to be known as the "spinal cord injury research trust fund."
2. The fund shall consist of all monies appropriated for its purpose, all monies required by this section or any other provision of law to be paid into or credited to such fund, and monies in an amount not to exceed eight million five hundred thousand dollars collected by the mandatory surcharges imposed pursuant to subdivision one of section eighteen hundred nine of the vehicle and traffic law. Nothing contained herein shall prevent the department of health from receiving grants, gifts or bequests for the purposes of the fund as defined in this section and depositing them into the fund according to law.
3. Monies of the fund, when allocated, shall be available for administrative costs of the spinal cord injury research board established pursuant to title four of article two of the public health law and for funding spinal cord injury research projects administered by such board.
4. Monies shall be payable from the fund on the audit and warrant of the state comptroller on vouchers approved and certified by the commissioner of health.

**Appendix II**  
**Bylaws of the Spinal Cord Injury Research Board**

**I. OFFICERS**

1. The officers of the Spinal Cord Injury Research Board (“Board”) shall be the Chair and Vice-Chair. The Chair is designated by the Governor. The Vice-Chair shall be selected by the Chair and shall serve for one year or until his or her successor has been selected.
2. The Chair may appoint a Board member to preside during the absence of the Chair and Vice-Chair from any meeting.

**II. DUTIES**

1. The officers of the Board shall perform the duties ordinarily associated with their respective offices.
2. The Chair shall be responsible for the general supervision of the work of the Board. The Chair shall represent the Board before the Governor, committees of the Legislature, or other public authorities, and may request any member or members to appear with him or her in his or her stead. The Chair shall preside at Board meetings.
3. The Vice-Chair, in the absence of the Chair, shall perform the duties of the Chair.

**III. CODE OF ETHICS AND CONFLICT OF INTEREST**

*Section 1. Code of Ethics.*

Members of the Board shall comply with Section 74 (Code of Ethics) of the Public Officers Law. No member of the Board should have any interest, financial or otherwise, direct or indirect, or engage in any business, transaction, or professional activity, or incur any obligation of any nature, which is in substantial conflict with the proper discharge of his or her duties as a Board member. Members should exercise their duties and responsibilities as Board members in the public interest of the inhabitants of the State, regardless of their affiliation with, or relationship to, any institution, organization, facility, agency, program, activity, category of provider, or interest group. The principles that should guide the conduct of Board members include, but are not limited to, the following:

- a) A Board member should endeavor to pursue a course of conduct that shall not raise suspicion among the public that he or she is likely to be engaged in acts that are in violation of his or her trust as a Board member.
- b) No Board member should permit his or her employment to impair his or her independence of judgment in the exercise of his or her duties as a Board member.

- c) No Board member should disclose confidential information acquired by him or her in the course of his or her duties as a Board member, or by reason of his or her position as a Board member, nor use such information to further his or her personal interests.
- d) No Board member should use, or attempt to use, his or her position as a Board member to secure unwarranted privileges or exemptions for himself or herself or others.
- e) No Board member should engage in any transaction as a representative or agent of the State with any business entity in which he or she has a direct or indirect financial interest that might reasonably tend to conflict with the proper discharge of his or her duties as a Board member.
- f) A Board member should not make personal investments in enterprises which may be directly involved in decisions to be made by him or her as a Board member or which shall otherwise create substantial conflict between his or her duty as a Board member to act in the public interest and his or her private interest.
- g) To preserve the public trust, Board members are prohibited during the tenure of their appointment from applying for or receiving support from the Spinal Cord Injury Research Trust Fund under Section 251 of the Public Health Law, or from having any role or interest (other than routine professional and collegial interest in the success of their institution or department) in proposals submitted for consideration by, or in research or proposals supported by, the Spinal Cord Injury Research Trust Fund.

*Section 2. Conflict of Interest – Applications and other Pending Matters.*

This section applies both to activities of the full Board and its committees.

a) **Absolute Disqualifications.**

When a Board or committee member, or his or her family has an interest, financial or otherwise, whether as owner, officer, director, fiduciary, employee, colleague, consultant, or supplier of goods or services, in an entity, institution, organization, facility, agency or program (hereafter collectively referred to as “entity”) whose application is before the Board or a committee of the Board for consideration or determination for a grant from the Spinal Cord Injury Research Trust Fund under Section 251 of the Public Health Law, that member shall (i) identify such interest to the Board or committee at any meeting when the application or request is to be considered, (ii) absent himself or herself from any portion of any meeting when such application is considered, and (iii) not participate in any vote of the Board or committee on such application. For purposes of this Article, “family” shall include a spouse, children, sibling, and any relative living in the member’s household.

b) **Disclosure and Possible Disqualification.**

When a Board or committee member, or his or her family member has (i) any of the above-noted interests in an entity the status of which might reasonably be affected by another entity whose grant application is before the Board or a committee of the Board, or (ii) when a member has any other interest or association which might reasonably be construed as tending to embarrass the Board or elicit public suspicion that he or she might be engaged in acts in violation of his or her trust as a Board member, the member shall disclose such interest or association at the time the application or other matter is formally considered by the Board or committee, so that the Chair and, if necessary, the Board or committee can then determine

whether the member's participation in the discussion or the vote on the application by the Board or by the committee or on the other matter would be proper.

c) Procedure.

Prior to the discussion of a grant application, the Chair of the Board and the Chair of the Committee shall request that Board members and committee members disclose all actual or potential conflicts and, when appropriate, explain the conflicts. In the case of conflicts constituting Absolute Disqualifications, the members with such conflicts shall immediately leave the meeting and remain absent during the period when the application is under consideration. In the case of conflicts constituting possible disqualifications, the Chair of the Board or Committee shall rule upon such conflicts subject to appeal by motion to the Board or committee that may override the Chair's decision by the affirmative vote of a majority of those present, excluding those members who are the subject of the vote.

d) Disclosure of Committee Interests to Board Meetings.

When the Chair of any committee reports the Committee's deliberations and recommendations on a matter to the Board, the Committee Chair shall indicate in the report all interests or associations disclosed by the committee members and state how such members voted with respect to the committee's recommendations.

e) Compliance with Public Officers Law.

Members of the Board shall comply with Sections 74 and 78 of the Public Officers Law as amended and the following rules governing conflicts of interest:

i) No member shall receive compensation in return for services rendered in relation to matters before any State agency if compensation is contingent upon action or failure to act by such State agency.

ii) No member of the Board who is also associated with any firm or association in which he/she has a specific interest shall sell any goods or services valued in excess of \$25 to any State agency unless pursuant to competitive bid.

iii) No member of the Board shall accept any gift (in excess of \$75) under circumstances in which it could reasonably be inferred that the gift was intended to influence him/her as a member of the Board.

iv) Members of the Board shall avoid any action which might result in or create the appearance of a conflict of interest.

f) Violation of Provisions.

If any member knowingly and intentionally violates these provisions, the Board or its Chair shall refer the matter to the Commissioner of Health for appropriate action.

#### **IV. EXECUTIVE SECRETARY**

The Board shall request the Department of Health to designate a Department employee as the Board's Secretary.

The Secretary shall prepare and send official notices of actions of the Board and shall administer the daily business of the Board under the general direction of the Chair. The

Secretary shall send a copy of the minutes of each meeting of the Board to each member of the Board ten business days prior to the next Board meeting. The minutes, as approved or corrected, shall serve as the official record of a meeting of the Board. Minutes shall be distributed or made available to the public after they have been approved by the Board. The Secretary shall make available records requested under the Freedom of Information Law and make announcements to the media and public of scheduled meetings as required by the Open Meetings Law.

## **V. MEETINGS OF THE BOARD**

### **a) Regular Meetings.**

The regular meetings of the Board shall be held at least two times per year but may be held more frequently as deemed necessary, subject to a call by the Chair or by request of a majority of the Board members, at a date, time and place approved by a majority of members, unless otherwise determined by the Board or by the Chair, who shall notify the Secretary at least ten business days in advance of the meeting.

### **b) Meeting Notification.**

The Secretary shall notify each Board member of Board meetings and shall send an agenda to his or her usual address not less than ten business days before the meeting.

### **c) Quorum.**

A majority (seven members) of the members of the Board (13 members) shall constitute a quorum for the transaction of any business or the exercise of any power or function of the Board and all matters requiring action shall be passed by a vote of a majority of the voting members of the Board. (A voting member abstaining from a vote shall be counted as present for the purpose of establishing a quorum.) Except as provided below, all meetings shall be conducted in accordance with Robert's Rules of Order Newly Revised, and a record of each vote shall be maintained. The normal method of voting shall be by roll call. A roll call vote on any question shall be taken by ayes and noes, abstentions noted, and a record of how each member voted entered in the Minutes.

### **d) Open Meetings.**

Meetings of the Board shall be noticed and conducted in accordance with the requirements of Article 7 (Open Meetings Law) of the Public Officers Law. Such meetings shall be open to the public except when otherwise provided by law. Guidelines for observers shall be adopted by the Board.

### **e) Public Comment Period.**

At least some portion of every regular Board meeting shall be set aside for public comment.

### **f) Order of Business.**

The order of business may be altered at the Chair's discretion or upon the request of a Board member. A portion of each Board meeting shall be set aside for the development of an agenda for the next Board meeting.

### **g) Absences.**

Any member, who fails to attend three consecutive meetings of the Board, unless excused by formal vote of the Board, shall be deemed to have vacated his or her position.

## **VI. COMMITTEES**

### **a) Standing Committees**

There shall be the following Standing Committee:

A *Scientific Review Committee* for the scientific and technical merit review of requests for proposals (grant applications).

The Chair of the Board shall appoint the members of Standing Committee and designate its Chair. In appointing members to the Standing Committee, the Chair will, to the extent practicable, ensure that the Committee comprises national or international experts of the highest scientific and technical caliber appropriate to spinal cord injury-related research while minimizing the potential for real or apparent conflict of interest. The term of committee membership shall be three years from the date of appointment. The Chair of the Board shall prescribe duties of the Standing Committee with approval by a majority of Board members.

### **b) Ad hoc Committees**

The Board may, at any time, appoint a special committee on any subject. All such special committees not previously discharged by the Board shall be considered discharged one year following their appointment, unless the Board shall move to continue them.

### **c) Committee Actions**

All committee matters requiring action or a formal recommendation shall be passed by a vote of a majority of the members appointed to serve on the committee.

When making a report to the Board, a committee should, in addition to reporting any recommendations of the majority of the committee, summarize any significant deliberations leading to such recommendations as well as opinions or recommendations of committee members who did not support the majority recommendations.

## **VII. PROPOSAL REVIEW PROCESS**

The Board shall establish merit review procedures to be used by the Scientific Advisory Committee which are modeled after the National Institutes of Health or the National Science Foundation as appropriate to the granting mechanisms the Board establishes.

## **VIII. OFFICE OF THE BOARD**

The official headquarters of the Board (at which the official copies of its Minutes, records, documents and other papers shall be kept) shall be at the offices of the Commissioner of Health at Albany, New York. The Secretary shall be responsible for the safekeeping of all Minutes, records, documents, correspondence and other items belonging to the Board. Every member of the Board and any other person duly authorized by a member shall have access at all times during the ordinary office hours of the Department of Health to all such Minutes, records, documents, correspondence and other items belonging to the Board; provided, however, that persons authorized by members shall not have access to records, documents, correspondence or other items that are exempt from disclosure or confidential under the Freedom of Information Law, the Personal Privacy Protection Law, or any other state or federal law. The Secretary shall designate some person to be in charge of all such Minutes,

records, documents, correspondence and other items belonging to the Board during his or her absence from the office.

#### **IX. AMENDMENT OF BYLAWS**

These Bylaws may be amended by the affirmative vote of the majority of the voting members of the Board at any regular or special meeting, provided that notice of the proposed amendment has been given at a prior meeting and that a copy of the proposed amendment has been sent by the Secretary to each member of the Board at least ten business days prior to the vote.

**Appendix III**  
**Publications and Presentations Reported in 2010**  
Resulting From Spinal Cord Injury Research Board-Funded Projects

**C019772**

Project Title:

**Winifred Masterson Burke Medical Research Institute**

A Novel Multimodality Approach to Treating Spinal Cord Injury, Center of Research Excellence

Haskew-Layton RE, Payappilly JB, Smirnova NA, Ma TC, Chan KK, Murphy TH, Guo H, Langley B, Sultana R, Butterfield DA, Santagata S, Alldred MJ, Gazaryan IG, Bell GW, Ginsberg SD and **Ratan RR**. "Controlled Enzymatic Production of Astrocytic Hydrogen Peroxide Protects Neurons From Oxidative Stress Via an Nrf2-Independent Pathway." *Proc Natl Acad Sci*. 2010; 107(40):17385-17390.

Ma TC, Campana A, Lange PS, Lee HH, Banerjee K, Bryson JB, Mahishi L, Alam S, Giger RJ, Barnes S, Morris SM, Jr., Willis DE, Twiss JL, Filbin MT and **Ratan RR**. "A Large-Scale Chemical Screen For Regulators of the Arginase 1 Promoter Identifies the Soy Isoflavone Daidzein as a Clinically Approved Small Molecule That Can Promote Neuronal Protection or Regeneration Via a cAMP-Independent Pathway." *J Neurosci*. 2010; 30:739-748.

**Ratan RR**. "Beyond Neuroprotection to Brain Repair: Exploring the Next Frontier in Clinical Neuroscience to Expand the Therapeutic Window for Stroke." *Transl Stroke Res*. 2010; 1:71-73.

Smirnova NA, Rakhman I, Moroz N, Basso M, Payappilly J, Kazakov S, Hernandez-Guzman F, Gaisina IN, Kozikowski AP, **Ratan RR**, and Gazaryan IG. "Utilization of an in vivo Reporter for High Throughput Identification of Branched Small Molecule Regulators of Hypoxic Adaptation. *Chem Biol*. 2010; 17:380-391.

Volpe BT, Huerta PT, Zipse J, Rykman A, Edwards D, Dipietro L, Hogan N and Krebs HI. "Robotics Devices as Tools to Develop a Stroke Phenotype." *Archives Neurol*. 2009; 66: 1086-1090.

**C020922**

Project Title:

**Regenerative Research Foundation (initially Albany Medical College)**

Engineering Embryonic Spinal Cord Stem Cells for SCI Repair

**Temple S**, "Engineering Embryonic Spinal Cord Stem Cells for SCI Repair." Presentation, World Stem Cell Summit, Detroit, Michigan, October 4, 2010.

**C020924**  
Project Title:

**Columbia University Medical Center**  
Bypassing Spinal Cord Injury to Promote Motor Function

**Martin JH**, Chakrabarty S, Uemura O, Drew T, Winfree CJ. "Monitoring Regenerating Connections With Indwelling Spinal Cord Electrodes in a Spinal Motor Bridge in the Cat." Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 19, 2009.

**C020925**  
Project Title:

**New York Medical College**  
Bystander Death in Traumatic Spinal Cord Injury

**Kang J**, Kang N, Yu Y, Zhang J, Petersen N, Tian GF, Nedergaard M. "Sulforhodamine 101 Induces Long-Term Potentiation of Intrinsic Excitability and Synaptic Efficacy in Hippocampal CA1 Pyramidal Neurons." *Neuroscience*. 2010; 169(4):1601-9.

**C020926**  
Project Title:

**Memorial Sloan-Kettering Cancer Center (initially New York University School of Medicine)**  
Genetic and MRI Studies of Spinal Cord Stem Cells

Nieman BJ, Shyu JY, Rodriguez JJ, Garcia AD, **Joyner AL**, Turnbull DH. "In vivo MRI of Neural Cell Migration Dynamics in the Mouse Brain." *NeuroImage*. 2010; 50:456-64.

Garcia AD, Eng L, Petrova R, **Joyner AL**. "Sonic Hedgehog Regulates Discrete Populations of Astrocytes in the Adult Mouse Forebrain." *J Neuroscience*. 2010; 30(41):13597-13608.

**Joyner AL**. Invited speaker, European Molecular Biology Organization meeting. "Hedgehog Signaling: From Developmental Biology to Anti-Cancer Drugs." Saint Jean Cap Ferrat, France, September 7, 2010.

**Joyner AL**, Invited speaker by graduate students for their Cellular and Molecular Biology lecture series, "Cell-Cell Communication: Secreted Factors and their Receptors." Ann Arbor, Michigan, November, 2009.

Garcia AD, Eng L, **Joyner AL**. "Sonic Hedgehog Signaling in the Adult Spinal Cord." Poster presentation, Neuroscience Scholars Program, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 18, 2009.

**C020927**  
Project Title:

**New York State Psychiatric Institute**  
Gene Expression After Acute and Chronic Injury and Rescue

Houle J, Ogata K, **Barr G**, Murray M. Neurons in Young Rats Respond Differently to Injury and Therapeutic Interventions From Those in Adults." Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

**C020929**  
Project Title:

**Stony Brook University, SUNY**  
Remyelination and Spinal Cord Injury

Relucio J, Tzvetanova I, Ao W, Lindquist S, and **Colognato H**. "Laminin Alters Fyn Regulatory Mechanisms and Promotes Oligodendrocyte Development." *J. Neurosci.* 2009; 29(38):11794-11806.

Tzvetanova I, McClenahan F, Osaka M, and **Colognato H**. "Helping to Start and Stop Myelination: Csk Has Dual Functions During Oligodendrocyte Development. European Meeting on Glial Cell in Health and Disease. Paris, France, September 9, 2009.

**Colognato, H**. "Sticking Around to Myelinate: The Role of Adhesion During Glial Cell Development." Virginia Commonwealth University, Richmond, Virginia, September 2009.

**C020931**  
Project Title:

**Upstate Medical University, SUNY**  
Local Release of Chondroitinase to Treat Spinal Injury

A. C. Conta Steencken and **Stelzner DJ**. "Loss of Propriospinal Neurons After Spinal Contusion Injury as Assessed by Retrograde Labeling." *Neuroscience.* 2010; 170(3): 971-980.

**C020932**  
Project Title:

**Wadsworth Center, New York State Department of Health**  
Using Reflex Conditioning to Restore Spinal Cord Function

Chen Y, Wang Y, Chenyou Sun, Chen L, English AW, Wolpaw JR and **Chen XY**. "H-reflex Up-Conditioning Encourages Recovery of EMG Activity and H-Reflexes After Sciatic Nerve Transection and Repair in Rats." *Journal of Neuroscience.* 2010; 30(48): 16128-16136.

Chen Y, Chen L, Liu RL, Wang Y, Wolpaw JR and **Chen XY**. "Effects of Soleus H-reflex Conditioning on Locomotor EMG and Kinematics." Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 14, 2010.

Wang Y, Chen L, Chen Y, Liu RL, Wolpaw JR and **Chen XY**. "Effects of Long-Term Sensorimotor Cortex (SMC) Stimulation on Spinal Cord Ventral Horn GABAA Immunoreactivity in Rats: Preliminary Results." Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 14, 2010.

Chen L, Chen Y, Liu RL, Wang Y, Wolpaw JR and **Chen XY**. "Effects of H-reflex Up-Conditioning in Rats With Lateral Column Contusion Injury." Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

**Chen XY**, Wang Y, Sun C, Chen L, Chen Y, Wolpaw JR and English AW. "Up-Conditioning of Rat Soleus H-reflex After Sciatic Nerve Transection and Regeneration May Increase Motoneuron VGLUT1 Terminals and GluR2/3 Immunoreactivity." Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

Liu RL, Chen Y, Chen L, Wang Y, Wolpaw JR and **Chen XY**. "Effects of Soleus H-reflex Conditioning on Hip, Knee, and Ankle Extensor and Flexor Muscles: Methods and Initial Results." Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

**C020933**

Project Title:

**College of Staten Island, CUNY**

Sensorimotor Control of Spinal Locomotor Centers in Human SCI

**Knikou M**. "Plantar Cutaneous Afferents Normalize the Reflex Modulation Patterns During Stepping in Chronic Human Spinal Cord Injury." *J Neurophysiol*. 2010; 103:1304-1314.

**C022046**

Project Title:

**Upstate Medical University, SUNY**

Neural Effects of Release of cABC and GDNF Caudal to SCI

**Osterhout DJ**. "Chondroitinase Treatment Promotes Greater Migration of Oligodendrocyte Progenitor Cells Following Spinal Cord Injury." Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 18, 2009.

**Osterhout DJ**. "Oligodendroglial Cells Express and Secrete Reelin." Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 18, 2009.

**C022047**

Project Title:

**Memorial Sloan-Kettering Cancer Center**

ADAM Proteinases in Spinal Cord Injury

Kolev M , Semavina M , Nikolov D, and **Saha N**. "Role of Ganglioside in Neuronal Regeneration and Spinal Cord Injury." Meeting abstract, Keystone Symposia, Synapses: Formation, Function and Misfunction. Snowbird, Utah, April 11-14, 2010.

**C022048**

Project Title:

**Downstate Medical Center, SUNY**

Neural Control of Force in a Brain-Machine Interface

Chhatbar PY, von Kraus LM, Semework M and **Francis JT**. "A Biofriendly and Economical Technique for Chronic Implantation of Multiple Microelectrode Arrays." *Journal of Neuroscience Methods*. 2010; 188(2):187-194.

Chhatbar PY, Semework M, Xu S, Marsh BT and **Francis JT**. "Force Control in a Brain-Machine Interface." 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

Chhatbar PY and **Francis JT**. "Comparison of Force and Power Generation Patterns and Their Predictions Under Different External Dynamic Environments (Code Sdwho)." Poster presentation, 32<sup>nd</sup> Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Buenos Aires, Argentina, September 1, 2010.

Chhatbar PY and **Francis JT**. "Real-time Control of Movements With Neural Signals Predicting Force-Related Variables." Poster presentation, AAPI National Convention. Washington, D.C., June 23, 2010.

DiStasio M and **Francis J**. "Linking Action and Perception in the Mammalian Thalamus." Fifth International Workshop, Statistical Analysis of Neural Data (SAND5). Pittsburgh, Pennsylvania, May 20, 2010.

Semework M, Xu S, Choi J and **Francis JT**. "Somatosensory Neuroprosthesis: Custom-Fitting Microstimulation Parameters." Poster presentation, Society for Neural Control of Movement 20<sup>th</sup> Annual Conference. Naples, Florida, April 21, 2010.

**C022057**

Project Title:

**Memorial Sloan-Kettering Cancer Center**

Manipulation of Glycans in Repair of Spinal Cord Injury

Ghosh M, Kim S-H, Melendez K, Tuesta LM, Puentes R, Maarouf AE, **Rutishauser U** and Pearse DD. "Genetically Altered Schwann Cells Improve Histological and Functional Restoration Following Transplantation Into Acute and Chronic Models of Spinal Cord Injury." Poster presentation, 13<sup>th</sup> International Symposium on Neural Regeneration. Pacific Grove, California, December 9-13, 2009.

Ghosh M, Kim S-H, Melendez K, Henao M, Patel S, Garcia M, Tuesta LM, Puentes R, Maarouf AE, **Rutishauser U** and Pearse DD. "PST-Expressing Schwann Cells Are Able to Migrate, Support Axon Growth and Improve Functional Outcome After Contusive SCI." Presentation, Neuroscience Research Day, University of Miami. Miami, Florida, November 20, 2009.

**C022058**

Project Title:

**Stony Brook University, SUNY**

Neurotrophins and Function of the Injured Spinal Cord

Hunanyan AS, Garcia-Alias G, Alessi V, Levine JM, Fawcett JW, Mendell LM and **Arvanian VL**. "Role of Chondroitin Sulfate Proteoglycans (CSPGs) in Axonal Conduction in Mammalian Spinal Cord. *J. Neuroscience*. 2010; 30(23):7761-7769.

Hunanyan AS, Hayrapetyan V and **Arvanian VL**. “Magnetic Stimulation Restores Conduction Deficits in Spared Fibers After Chronic Thoracic Hemisection and Contusion Injuries of Spinal Cord in Adult Rat.” Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 16, 2010.

**Arvanian VL** and Hunanyan AS. “Properties of Action Potential That Determine Diminished Excitability After Chronic Spinal Cord Hemisection: *in vivo* Intra-Axonal Recording From Lateral White Matter in Adult Rat.” Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 14, 2010.

Alessi V, Hunanyan A, Matthews G, Pearse D, and **Arvanian VL**. “Changes in the Pattern of Sodium Channel Na<sub>v</sub>1.6 Expression in Axons Contralateral to Chronic Hemisection of the Spinal Cord in Adult Rats.” Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

Collier LM, Hunanyan AS, Alessi VA, Tolpygo AS, Leesha K, Lou L, Mendell LM, Schnell L, Robinson JK and **Arvanian VL**. “Quantitative Evaluation of Behavioral and Physiological Impairments After Chronic Hemisection of Adult Rat Spinal Cord.” Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 19, 2009.

Hunanyan AS, Garcia-Alias G, Alessi VA, Fawcett JW, Levine JM, Mendell LM and **Arvanian VL**. “Diverse Effects of CSPGs on Conduction in Adult Rat Spinal Cord.” Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 18, 2009.

**C022062**

Project Title:

**Nathan S. Kline Institute for Psychiatric Research**

Aquaporin-4 Water Channels in Spinal Cord Injury

Kimura A, Hsu M, Seldin M, **Scharfman HE** and Binder DK. “Protective Role of Aquaporin-4 Water Channels Following Contusion Spinal Cord Injury.” Poster presentation, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 21, 2009.

**C022064**

Project Title:

**Columbia University Medical Center**

Harnessing Corticospinal Activity to Promote Motor Recovery

Li Q, Brus-Ramer M, **Martin JH** and McDonald JW. “Electrical Stimulation of the Medullary Pyramid Promotes Proliferation and Differentiation of Oligodendrocyte Progenitor Cells in the Corticospinal Tract of the Adult Rat.” *Neuroscience Letters*. 2010; 479(2): 128-133.

Carmel JB, Berrol LJ, Brus-Ramer M and **Martin JH**. "Chronic Electrical Stimulation of the Intact Corticospinal System After Unilateral Injury Restores Skilled Locomotor Control and Promotes Spinal Axon Outgrowth." *J. Neuroscience*. 2010; 30:10918-10926.

Carmel JB, Berrol L, Brus-Ramer M and **Martin JH**. "Chronic Electrical Stimulation of the Intact Corticospinal System After Unilateral Injury Restores Skilled Locomotor Control and Promotes Spinal Axon Outgrowth." Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 16, 2010.

Carmel JB, Kim S, Brus-Ramer M and **Martin JH**. "Rats Preshape the Reaching Paw to the Target: Evidence for Feed-Forward Motor Control Mediated by the Corticospinal Tract." Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 16, 2010.

**Martin JH**. "Challenges and Opportunities of Activity-Dependent Plasticity." Presentation, Neural Interfaces Conference. Long Beach, California, June 22, 2010.

**Martin JH**. "Harnessing Activity-Dependent Plasticity to Reconstruct Damaged Corticospinal System Circuits." Presentation, First International Workshop on Synaptic Plasticity: From Bench to Bedside. Taormina, Italy, April 28, 2010.

Carmel JB, Berrol L and **Martin JH**. "Electrical Stimulation of the Spared Corticospinal System After Unilateral Injury Restores Skilled Locomotion." Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 21, 2009.

**C022065**  
Project Title:

**Upstate Medical University, SUNY**  
Neuronal Response of Propriospinal Neurons to SCI

Conta Steencken AC, Siebert JR, **Stelzner DJ**. "Lack of Axonal Sprouting of Spared Propriospinal Fibers Caudal to Spinal Contusion Injury is Attributed to Chronic Axonopathy." *J. Neurotrauma*. 2009; 26: 2279-2297.

Conta Steencken, AC and **Stelzner, DJ**. "Loss of Propriospinal Neurons After Spinal Contusion Injury as Assessed by Retrograde Labeling." *Neuroscience*. 2010; 170(3): 971-980.

Siebert JR, Middleton FA and Stelzner, DJ. "Intrinsic Response of Thoracic Propriospinal Neurons to Axotomy." *BMC Neuroscience*. 2010a; 11:69.

**C022067**

Project Title:

**Rensselaer Polytechnic Institute**

Guided Neuronal and Glial Migration in Electrically Conductive Collagen-Carbon Nanotube Scaffolds

Behan B, DeWitt DG, Bogdanowicz DR, Bale SS, Koppes AN and **Thompson DM**. "Single-Walled Carbon Nanotubes Alter Schwann Cell Behavior Differentially Within 2D and 3D Environments." *Journal of Biomedical Materials Research*. 2010; doi: 10.1002/jbm.a.32939.

DeWitt D, Kazuba S, **Thompson D** and Stegemann J. "Schwann Cell Number and Process Extension Are Enhanced Within 3-D Collagen-Matrigel™ Composite Scaffolds." *Tissue Engineering*. 2009; 15(10):2785-93.

**Thompson DM**. "Development of a Multi-Cue Scaffold for Neural Tissue Engineering." Presentation. CUNY, City College of New York, Department of Biomedical Engineering. New York, New York, October 28, 2009.

Eldridge AN and **Thompson DM**. "Alignment of Primary Neonatal Rat Schwann Cells in Applied Electric Fields." Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 17, 2009.

**D.M. Thompson**. "Development of a Multi-Cue Scaffold for Neural Tissue Engineering." Presentation, CUNY, City College of New York, Department of Biomedical Engineering. New York, New York, October 10, 2009.

Eldridge AN and **Thompson DM**. "Applied Physiologic Electric Fields Orient Primary Neonatal Rat Schwann Cells." Meeting abstract, Biomedical Engineering Society Annual Meeting. Pittsburgh, Pennsylvania, October 8, 2009.

**C023680**

Project Title:

**Regenerative Research Foundation**

Human Neural Stem Cell Cultures From Adult Spinal Cord

**Yan J**. "Organotypic Culture Enhances Proliferation of Adult Human Cadaveric Spinal Cord Progenitor Cells." Meeting abstract, 8<sup>th</sup> Annual International Society for Stem Cell Research Meeting. San Francisco, California, June 16-19, 2010.

**C023681**

Project Title:

**Stony Brook University, SUNY**

Functions of Atypical Protein Kinase C in Axon Regeneration

Hunanyan A, Garcia-Alias G, Alessi V, **Levine JM**, Fawcett JW, Mendell LM and Arvanian V. "Role of Chondroitin Sulfate Proteoglycan in Axonal Conduction in Mammalian Spinal Cord." *J Neurosci*. 2010; 30(23): 7761-7769.

Lee SI and **Levine JM**. "Functions of Atypical PKC and the PAR Complex in Axonal Growth Inhibition." Meeting abstract, Cold Spring Harbor Axon Guidance Meeting, Cold Spring Harbor, New York, September 21-25, 2010.

**Levine JM**. "Functions of Atypical PKC $\zeta$  and the Par Complex in Axon Growth Inhibition." Meeting abstract, 43<sup>rd</sup> Winter Conference on Brain Research. Breckenridge, Colorado, January 23-29, 2010.

**C023683**

Project Title:

**Stony Brook University, SUNY**

Bladder-Sphincter Dyssynergia: Role of Intrinsic Motoneuron Properties

**Collins WF**. "External Urethral Sphincter Motor Unit Recruitment During Micturition in the Rat." Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 20, 2009.

**Collins WF**. "Effect of Spinal Cord Transection on the Time Course of External Urethral Sphincter Activation in the Rat." Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 18, 2009.

**C023684**

Project Title:

**College of Staten Island, City University of New York (CUNY)**

The Combined Effect of Acrobatic and Magnetic Stimulation on SCI

**Ahmed Z**, Freedland R and **Wieraszko A**. "Excitability Changes in the Sciatic Nerve and Triceps Surae Muscle After Spinal Cord Injury in Mice." *Journal of Brachial Plexus and Peripheral Nerve Injury*. 2010; 5:8.

**Ahmed Z**. "Dipolar Cortico-Muscular Electrical Stimulation: A Novel Method That Enhances Motor Function in Both Normal and Spinal Cord Injured Mice." *Journal of NeuroEngineering and Rehabilitation*. 2010; 7: 46.

**Ahmed Z**, Wagdy M, Benjamin M, Mohamed S, Mohamed H, Ahmed S, Kanjilal B. and **Wieraszko A**. "Therapeutic Effects of Acrobatic Exercise and Magnetic Field Exposure on Functional Recovery After Spinal Cord Injury in Mice." *Bioelectromagnetics*. 2010; Epub ahead of print.

**Wieraszko A and Ahmed Z**. "The Influence of Magnetic Stimulation on Turnover of Neurotransmitter and Calcium in Neuronal Preparations." 6<sup>th</sup> International Workshop on the Influence of Magnetic Fields on Biological Systems. Meeting presentation, Bodrum, Turkey, October 10-14, 2010.

**Ahmed Z and Weiraszko A**. "Electrical Stimulation Device for Motor Function Recovery (Including Spinal Cord Injury)." Presentation and meeting abstract, NYC Emerging Medical Technologies Summit at Columbia University. New York City, New York, March 26, 2010.

**Ahmed Z.** “Disruption of Patterned Spinal Activity Following Acute Contusive Spinal Cord Injury.” Presentation, Neuronal Circuits Cold Spring Harbor Laboratory Winter Conference. Cold Spring Harbor, New York, March 11, 2010.

**Ahmed Z.** “Contusive Spinal Cord Injury Causes Permanent Alteration to Rhythmogenic Circuits in Adult Mice.” Poster presentation, Neuronal Circuits Cold Spring Harbor Laboratory Winter Conference. Cold Spring Harbor, New York, March 11, 2010.

**C023685**

Project Title:

**Helen Hayes Hospital**

EMG/EEG Training to Improve Motor Function after Spinal Cord Injury

Abel B, Pomerantz F, DeFrancesco E, Lichtman SW and **Thompson AK.** Operant Up-Conditioning of the Ankle Dorsiflexor Motor Evoked Potentials in People with Chronic Incomplete Spinal Cord Injury.” Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

Pomerantz F, Wolpaw JR, Lichtman SW, Abel B, DeFrancesco E and **Thompson AK.** “Operant Down Conditioning of the Soleus H-Reflex in People with Spasticity Due to Chronic Incomplete Spinal Cord Injury.” Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13 2010.

**Thompson AK,** Abel B and Wolpaw JR. “Soleus H-Reflex Modulation During Locomotion in People with Chronic Incomplete Spinal Cord Injury.” Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

Makihara Y, **Thompson AK,** Abel B and Segal RL. “Operant Down-Conditioning of Soleus H-Reflex in Humans: Effects on Synergist Muscles.” Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

Segal RL, Makihara Y, Abel B and **Thompson AK.** “Effects of Operant Conditioning of Soleus H-Reflex on Locomotion.” Meeting abstract, 40<sup>th</sup> Annual Meeting of the Society for Neuroscience. San Diego, California, November 13, 2010.

Pomerantz F, Wolpaw JR, Lichtman SW, DeFrancesco E and **Thompson AK.** “Operant Conditioning of the Soleus H-Reflex in Spastic Subjects After Incomplete Spinal Cord Injury.” Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 17, 2009.

**Thompson AK**, DeFrancesco E, Lichtman SW and Pomerantz F. "Operant Conditioning of Motor Evoked Potentials to Transcranial Magnetic Stimulation in People With Chronic Incomplete Spinal Cord Injury." Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 17, 2009.

Tenteromano L, Duffield M, Pomerantz F and **Thompson AK**. "Repetitive Common Peroneal Stimulation Increases Ankle Dorsiflexor Motor-Evoked Potentials in People with Incomplete Spinal Cord Injury." Meeting abstract, 39<sup>th</sup> Annual Meeting of the Society for Neuroscience. Chicago, Illinois, October 17, 2009.

**C023687**

Project Title:

**New York University School of Medicine**

Removing Microglia From Glial Scar Following Spinal Cord Injury

**Yang G**, Pan F, Parkhurst CN, Grutzendler J and **Gan W-B**. (2010) "Thinned-Skull Cranial Window Technique for Long-Term Imaging of the Cortex in Live Mice." *Nat Protoc*. 2010; 5(2): 201-8.

Parkhurst CN and **Gan W-B**. "Microglia Dynamics and Function in the CNS." *Curr Opin Neurobiol*. 2010; 20(5): 595-600.

Pan F, Aldridge GM, Greenough WT and **Gan W-B**. (2010) "Dendritic Spine Instability and Insensitivity to Modulation by Sensory Experience in a Mouse Model of Fragile X Syndrome." *PNAS*. 2010; 107(41): 17768-17773.

**C023688**

Project Title:

**New York University School of Medicine**

CXCR6 and Central Nervous System Injury

**Kim JV**, Jiang N, Tadokoro CE, Liu L, Ransohoff RM, Lafaille JJ and Dustin ML. "Two-Photon Laser Scanning Microscopy Imaging of Intact Spinal Cord and Cerebral Cortex Reveals Requirement for CXCR6 and Neuroinflammation in Immune Cell Infiltration of Cortical Injury Sites." *J Immunol Methods*. 2010; 352(1-2):89-100.

**Kim JV**. "Central Nervous System Injury Imaging and Neuropathology." Presentation, University of Freiburg School of Medicine, Freiburg, Germany, September 2010.

**Kim JV**, Kang SS, Dustin ML and McGavern DB. "Myelomonocytic Cell Recruitment Causes Fatal CNS Vascular Injury During Acute Viral Meningitis." *Nature*. 2009; (457):191-195.

**Kim JV**. "Central Nervous System Injury Imaging: Vaccine and Inflammation." Presentation, Trudeau Institute, Saranac Lake, New York, May 2010.

**Kim JV.** “Central Nervous System Injury Imaging.” Presentation, Uniformed Services University Department of Pharmacology, Traumatic Brain Injury Center. Bethesda, Maryland, March 2010.

**Kim JV.** “Central Nervous System Injury Imaging: Vaccine and Inflammation.” Presentation, University of Rochester School of Medicine. Rochester, New York, January 2010.

**C023689**

Project Title:

**Hunter College, CUNY**

Targeting Soluble AC for the Recovery of Spinal Cord Injury

Perdigoto AL, Chaudhry N, Barnes GN, **Filbin MT** and Carter BD. “A Novel Role for PTEN in the Inhibition of Neurite Outgrowth by Myelin-Associated Glycoprotein in Cortical Neurons.” *Mol Cell Neurosci*. In press.

**C023690**

Project Title:

**College of Staten Island, CUNY**

Mechanisms Underlying Locomotor Recovery After Step Training in SCI

**Knikou M.** “Soleus H-Reflex Phase-Dependent Modulation During One-Legged Foot Reaching and Withdrawal in Standing Humans.” *Neuroscience Letters*. 2010; Epub ahead of print.

**Knikou M.** “Neural Control of Locomotion and Training-Induced Plasticity After Spinal and Cerebral Lesions.” *Clinical Neurophysiology*. 2010; 121(10): 1655-1668.

**Knikou M.** “Segmental Interneuronal Locomotor Circuits in Human Spinal Cord Injury During Assisted Stepping.” Research Seminar Series presentation, University Pierre and Marie Curie and Pitie Salpetriere Hospital. Paris, France, May 20, 2010.

**Knikou M.** “Soleus H-Reflex Excitability Changes in Spinal Intact and Injured Subjects at Rest and During Locomotion.” Lecture, 21<sup>st</sup> Meeting of the American Society of Neurophysiological Monitoring. Nashville, Tennessee, April 23, 2010.

**C023691**

Project Title:

**University of Rochester**

Specific Astrocyte Subtypes for SCI Repair Without Allodynia

**Mayer-Pröschel M.** “Astrocytes in Disease and Injury.” Women in Neuroscience Lecture, W.M. Keck Center for Collaborative Neuroscience, Rutgers University. Piscataway, New Jersey, October 2009.

Strathmann F, Mihaila C, Luebke A and **Mayer-Pröschel M.** “CNS Myelin-Induced Auditory Brainstem Response Latency and the Characterization of Transplantable Precursors.” Meeting abstract, Upstate New York American Association for Clinical Chemistry meeting. Rochester, New York, April 30, 2009.

**C023832**

Project Title:

**Weill Medical College of Cornell University**

Synthesis and Evaluation of NAD-Augmenting Agents for Spinal Cord Injury

**Suave A.** “Sirtuin Chemical Mechanisms.” *Biochimica et Biophysica Acta.* 2010; 1804:1591-1603.

## Appendix IV

### Patent Applications Reported in 2010 Resulting from Spinal Cord Injury Research Board-Funded Projects

<b>C023691</b>	<b>University of Rochester</b>
Project Title:	Specific Astrocyte Subtypes for SCI Repair Without Allodynia
12/596,223	Telencephalic Glial-Restricted Cell Populations and Related Compositions and Methods
<b>C023684</b>	<b>College of Staten Island, CUNY</b>
Project Title:	The Combined Effect of Acrobatic and Magnetic Stimulation on SCI
PCT/US10/53720	Dipole Electrical Stimulation Employing Direct Current for Recovery From Spinal Cord Injury

**Appendix V**

**Statements Provided to the Board During 2010 Board Meetings**

December 3, 2010

**STATEMENT TO THE SPINAL CORD INJURY RESEARCH BOARD BY TERRY O'NEILL, ESQ. (transcript)**

Thank you very much.

I like to cultivate a reputation for not having a whole lot to say and getting my business done quickly. Yesterday I had the interesting experience of meeting with a number of people with the Division of the Budget who are putting together the public protection budget with all our corrections and police agencies, and they have not gotten so much as a word of marching orders from the incoming Cuomo administration as to what is going to be in that budget. And, as has been said here today, there has to be something on paper to be delivered to the legislature by the end of January; they have a constitutional obligation to do that. So we had a very interesting discussion about, you know, that they don't know what to do. But here we have, you know, a program that is very important to me and I consider it a part of a whole panoply of public protection legislation that I have written over the years with the help of people like Paul Richter and others that you wouldn't know about. We have found creative ways to use the public safety system in this state to, in some instances, undo the damage that's caused by crime. And we all know that Paul was shot by a would-be gun trafficker, we have a lot of people who are hurt every year as a result of gun violence and certainly the largest number of people that have spinal cord injuries in this state are as a result of traffic accidents.

So what we did some years ago, twelve years ago, was to put all of our police services in New York to work raising a little bit of money to invest in undoing the damage that happens out of traffic accidents, out of violent crime. And today what we're finding increasingly, this is numbers I get from the New York Times, is that a very large number of our casualties that are coming back from our wars in the Middle East are people with brain injury and spinal cord injury, so there's ever so much more impetus to be investing in basic neurological research that will find the cures and treatments for all of these casualties and injuries. And I believe that when we created this program here in New York, we created something that provided an incredible focus on solving the fundamental problem of the fact that a neuron that is damaged in spinal cord injury doesn't regenerate. And we didn't accept that that was the end of the story, that we were going to fund research to take care of that problem and in doing that, we would be pushing along opportunities to have advancements in all sorts of other neurological problems that people face in their lives and indeed, you know, as I've seen, you know, for a number of years.

Although I wrote the bill that created this program, it seemed to be running very well for a long time until this year's budget crisis; this is the first time I got a chance to look at everything that has been accomplished in so many areas of research, and it is an extraordinarily worthwhile program. Now within a few weeks the Governor is going to send over a budget to be considered and it will be his healthcare budget among other things. And I will be there, I know, for the public protection budget to testify and I'll certainly be talking about this program, and if we need to again as we did last year, we got a bunch of people together to testify when the Governor's healthcare budget was there. Now I don't expect the same thing to happen as happened last year because the Governor took extraordinary action and just forced the Legislature to vote on a healthcare budget that took away the money from this program. That I do not believe is going to happen this coming year. So we have to be ready when I go to the public protection hearing, when others who are colleagues go to the public health budget

hearing, to talk about this program and exactly what we have gotten for our money over these years and what exactly we propose to do and to make a very, very powerful case that this is an investment in industry and of the future for our state of New York, in biotechnology or whatever you want to call it.

Now we have a tremendous number of medical research facilities in this state and we have gotten them focused for twelve years now on a very specific problem that is having all kinds of wonderful implications in the direction of which research is going. And as we were telling people when lobbying this year that Acorda Therapeutics got approved a drug that is, I'm told, is worth a billion dollars a year. That is an investment that comes out of this program and that is why both houses of the legislature and the next governor should be telling us that this is a very important investment in New York's future and the work that you're doing around this table and keeping it going and making sure that when whatever happens with the budget this year, whatever resources we have are properly invested, that we're going to have the kind of success that we've all been dreaming about all this time. So I think that's five minutes.

December 3, 2010

## **OPEN LETTER TO THE SPINAL CORD INJURY RESEARCH BOARD MEMBERS: PROFESSIONAL MISCONDUCT BY THE JUNE 2005 REVIEW PANEL**

### **Preliminary Statement**

Most papers and reviews on pre-clinical studies in spinal cord injury (SCI) maintain the dogma that “*no effective therapeutic interventions exist for severe spinal cord injury.*” While currently true for human injury, in the pre-clinical setting, published data show that an effective curative procedure for complete transection<sup>1,2,3</sup> and severe crush spinal cord injury<sup>4,5</sup> has been developed using the conventional clinical procedure radiation therapy. Nevertheless, these data have been ignored by the SCI investigators who concurrently also perpetuate misconceptions and superstition that radiotherapy is toxic/lethal. Consequently the translation of this experimental procedure into a treatment to prevent paralysis in acute human injury has been knowingly hampered/prevented.

### **Open Letter: Call for Responsibility and Oversight**

Radiotherapy<sup>6</sup> is a life-saving clinical modality used specifically to eradicate solid tumors. Radiotherapy of the SCI-site can facilitate restoration of structure<sup>1,3</sup> and of brain-controlled motor function<sup>2</sup> below the lesion. It eradicates cells that interfere with natural repair following injury<sup>1</sup>, and is effective only if applied within the critical period, 2-3 weeks postinjury. Furthermore, combining radiotherapy with training in severe contusion<sup>5</sup> resulted in significant restoration of standing and stepping capacities [appendix #1]. Nevertheless, a grant proposal entitled “Teaching the Repaired Contused Spinal Cord to Walk” submitted to the NYS SCRIB that was aimed at improving training protocols and independent walking capacity following repair was rejected because ‘radiotherapy is lethal’, citing the study of Ridet *et al.*<sup>7</sup>, in which the SCI animals died indiscriminately, not due to the irradiation but due to the inhumane negligent care. As discussed below, each of panel members is personally and directly responsible for depriving a cure from the victims of spinal cord injury. Each member of the

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<sup>1</sup> Kalderon, Fuks (1996a) Structural recovery in lesioned adult mammalian spinal cord by x-irradiation of the lesion site, *PNAS* **93**:11179

<sup>2</sup> Kalderon, Fuks (1996b) Severed corticospinal axons recover electrophysiologic control of muscle activity after x-ray therapy in lesioned adult spinal cord, *PNAS* **93**:11184

<sup>3</sup> Kalderon, Xu, Koutcher, Fuks (2001). Fractionated radiation facilitates repair and functional motor recovery after spinal cord transection in rat. *Brain Res.*, **904**:199.

<sup>4</sup> Kalderon, Muruganandham, Koutcher, Potuzak, (2007) Therapeutic strategy for acute SC contusion injury: Cell elimination combined with microsurgical intervention, <http://dx.plos.org/10.1371/journal.pone.0000565>

<sup>5</sup> Ichiyama, Potuzak, Balak, Kalderon, Edgerton (2009) Enhanced Motor Function by Training in Spinal Cord Contused Rats Following Radiation Therapy, <http://dx.plos.org/10.1371/journal.pone.0006862>

<sup>6</sup> Radiotherapy, involves repetitive daily doses of irradiation at the range of 2-4 Gy given usually over a course of several weeks; employing total doses that eradicate tumors without exceeding the normal tissue tolerance. For example, the clinical tolerance dose values for the human spinal cord are 45-50 Gy and 33 Gy when delivered in daily fractions of 2Gy and 3 Gy, respectively

<sup>7</sup> Ridet *et al.* (2006) Effects of spinal cord X-irradiation on the Recovery of Paraplegic Rats, *Exp Neurol* **161**:1

SCRIB having this information at hand should determine for himself/herself which role and responsibility he/she takes.

**The Scientific Misconduct of the June 2005 Review Panel Headed by Dalton Dietrich**

In the December 3, 2010 meeting of the SCI Research Board I would like to alert and present the Board with a glimpse into the reckless review made by a panel<sup>8</sup> of 18 investigators headed by Dr. Dalton Dietrich, the Scientific Director of the Miami Project to Cure Paralysis. This panel faulted my research, declaring that the 'radiation therapy doses' that is used for decades by the most advanced clinical institutions to treat cancer and save millions of lives, leads to 'high rate mortality' as demonstrated by Ridet *et al*<sup>7</sup>. Most disturbing, the panel made this statement without reading and examining the data and the facts in that paper; the panel stated under the **Translational Clinical Potential** section:

The **doses used** in this study **are extremely high** and are doses that **other investigators** have **shown** to have **high rates of mortality**. The Principal Investigator cites the Ridet abstract but not the manuscript where these contradictory data are detailed. . . . No data are presented on the mortality rates with present doses and **a discussion of the discrepancies between other published data are absolutely necessary.**

A close examination shows that Ridet *et al*<sup>7</sup>, could not find any causal statistical relationship between radiation dose and death incidence, they admitted that the entire conclusion of the paper has no scientific validity:

*Mortality.* Some animals died after irradiation. . . . High doses tended to be associated with mortality, but **no statistically significant relationship between survival rate and X-irradiation dose was found** ( $P = 0.21$ ) in the likelihood ratio test, probably due to a lack of power.

On the other hand examining the Methods section shows the real cause for high mortality inhumane treatment and negligence in postsurgery care the SCI animals that emptying the bladder was done only once a day and then 2 weeks postinjury only once every other day the rats suffered from bladder infections

*Spinal cord injury.* . . . The animals were sutured and housed individually in large boxes. Every day for 2 weeks, they were visited and manual bladder expression performed. An intramuscular injection of antibiotics (gentamycin, 0.2 mg/100 g bw, i.m.) was given if the urine was not clear. The animals were then visited every other day for the last 2 weeks, and the same treatment was administered.

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<sup>8</sup> **Review Panel: Chairperson:** Dalton Dietrich, Ph.D., Scientific Director, The Miami Project to Cure Paralysis Mehmet Bilgen, Ph. D.; Fernando Gomez-Pinilla, Ph.D.; Phil Horner, Ph.D.; Charles Hubscher, Ph.D.; John Kern, M.D.; Donald Marion, M.D.; Andrew McClellan, Ph.D.; Gordon Mitchell, Ph.D.; Olivera Nesic-Taylor, Ph.D.; Peter Ohara, Ph.D.; Steve Perlmutter, Ph.D.; Paul Reier, Ph.D.; William Rymer, M.D., Ph.D.; Samuel Saporta, Ph.D.; Nicholas Seeds, Ph.D.; Riyi Shi, M.D., Ph.D.; David Shine, Ph.D.; Scott Whittemore, Ph.D.

**Concluding Remarks**

A comprehensive examination of the panel's review and discussion of the role each of the panel members has in knowingly preventing cure from the victims of spinal cord injury will be completed shortly and provided to the members of the SCIRB. Enclosed here are: portions of the review rendered by the panel in June 2005 [appendix, #2]; and part of the Ridet et al paper and some data related [appendix, #3] for your examination.

Thank you for your attention.

Sincerely,

Nurit Kalderon, Ph.D.

cc: Dalton Dietrich, Ph.D., Mehmet Bilgen, Ph. D.; Fernando Gomez-Pinilla, Ph.D.; Phil Horner, Ph.D.; Charles Hubscher, Ph.D.; John Kern, M.D.; Donald Marion, M.D.; Andrew McClellan, Ph.D.; Gordon Mitchell, Ph.D.; Olivera Nestic-Taylor, Ph.D.; Peter Ohara, Ph.D.; Steve Perlmutter, Ph.D.; Paul Reier, Ph.D.; William Rymer, M.D., Ph.D.; Samuel Saporta, Ph.D.; Nicholas Seeds, Ph.D.; Riyi Shi, M.D., Ph.D.; David Shine, Ph.D.; Scott Whittemore, Ph.D.

## Glossary of Abbreviations

aPKC	atypical protein kinase C
ATP	adenosine triphosphate
BBB	Basso, Beattie and Bresnahan
BMI	brain-machine interface
BMP	bone morphogenetic protein-4
cABC	chondroitinase ABC
cAMP	cyclic adenosine monophosphate
CSPGs	chondroitin sulfate proteoglycans
CART	Collaborations to Accelerate Research Translation
CNS	central nervous system
col-CNT	collagen and carbon nanotube scaffolds
col-Matrigel	three-dimensional type 1 collagen-Matrigel™
CSPG	chondroitin sulfate proteoglycans
CUNY	City University of New York
Cx	connexins
Cx43	connexin 43
EEG	electroencephalogram
EF	electric field
EUS	external urethral sphincter
GDA	glial-restricted precursor derived astrocytes
GDNF	glial-derived neurotrophic factor
GRPs	glial-restricted precursor cells
IDEA	Innovative, Developmental or Exploratory Activities
MARCKS	myristoylated alanine-rich C kinase substrate
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NAD	nicotinamide adenine dinucleotide
NR2D	N-methyl-D-aspartate receptor 2d
NT-3	neurotrophin NT-3
NIH	National Institutes of Health
NMDA	<i>N</i> -methyl <i>D</i> -aspartate
NSCs	neural stem cells
PI	principal investigator
PS	proprio-spinal
RFA	Request for Applications
SCI	spinal cord injury
SCIRB	Spinal Cord Injury Research Board
Shh	sonic hedgehog growth factor
SUNY	State University of New York
SWCNT	single-walled carbon nanotubes