

**State of New York**

**Spinal Cord Injury  
Research Board**

**2007  
Annual Report**

**April 21, 2008**



**NEW YORK STATE SPINAL CORD INJURY RESEARCH BOARD**

**Roster of Members  
As of December 31, 2007**

**Lorne Mendell, Ph.D., Chair**  
State University of New York  
at Stony Brook

**Barbara S. Koppell, M.D.**  
Metropolitan Hospital Center

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

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

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

**Paul Richter**  
Spinal Cord Society

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

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

**Deborah A. Hrustich, M.D.**  
Albany-Troy Neurosurgical Associates, P.C.

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

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

**New York State Department of Health Staff**

**Teresa K. Ascienzo**  
Associate Accountant  
Office of Extramural Grants Administration  
Wadsworth Center

**Bonnie Jo Brautigam**  
SCIRB Executive Secretary to the Board,  
and Director, Office of Extramural Grants  
Administration  
Wadsworth Center

**Luba Goldin**  
Laboratory Center Administrator 1  
Office of Extramural Grants Administration  
Wadsworth Center

**Michael Heeran**  
Health Program Administrator 2  
Office of Extramural Grants Administration  
Wadsworth Center

**Nora Prall**  
Administrative Aide  
Contracts Unit  
Wadsworth Center

**Lani Rafferty**  
Health Program Administrator 1  
Office of Extramural Grants Administration  
Wadsworth Center

## Executive Summary

In July 1998, landmark legislation was enacted to create the New York State Spinal Cord Injury Research Board (SCIRB) and allocate funding to the Spinal Cord Injury Research Trust Fund. The purpose of the fund is to assist leading researchers with ongoing and new efforts to find a cure for spinal cord injuries. The Board consists of 13 members appointed by the Governor and legislative leaders. SCIRB was first convened in August 1999. The Board is primarily responsible for overseeing a research grants program, financed by the Spinal Cord Injury Research Trust Fund, to support proposals from leading scientists, physicians and other experts who are dedicated to finding a cure for spinal cord injuries. The Board is to report annually to the Governor and Legislature on its grant-related activities, the status of Board-supported research and on the Trust Fund.

The Board is grateful to the Governor and the Legislature for the funding to support its mission.

The salient accomplishments of the Board and its Program in 2007 follow:

- On October 31, 2007, the Spinal Cord Injury Research Board issued a Request for Applications (RFA) to solicit applications for five research funding mechanisms: Collaborations to Accelerate Research Translation (CART); Innovative, Developmental or Exploratory Activities (IDEA) projects; Postdoctoral Fellowships; and Mentored Research Scientist and Mentored Clinical Scientist Development Awards. The estimated start date of contracts awarded through this RFA is October 1, 2008. Obligations resulting from these multiyear awards are expected to total \$7.5 million. It is the intent of SCIRB to issue this RFA on a yearly basis beginning in May 2008, with a contract start date of the following July.
- On November 7, 2007, SCIRB issued a Program Project RFA, to fund several interdependent research projects, a mechanism that offers significant scientific advantages to supporting these same projects as individual research grants. Successful Program Projects are expected to establish effective collaborations, particularly in emerging areas of research, that extend beyond the life of the Program Project award itself. The estimated start date of the Program Project contracts is January 1, 2009. Obligations resulting from these multiyear awards are estimated to total \$6 million. SCIRB intends to issue this RFA on a biennial basis in January, with a contract start date of the following January.
- Several Board member vacancies were filled during 2006; only two positions now remain to be filled by the Speaker of the Assembly and the Senate Minority Leader.

- Late in 2007, an additional staff position was created to support the Spinal Cord Injury Research Board Program. Also, a temporary staff person was hired to initiate an evaluation of previously funded research.

During 2007, a total of 20 papers, one textbook chapter and numerous abstracts stemming from 12 of 52 SCIRB-funded projects active in 2007 were published or are accepted for publication (Appendix III). Notably, 22 of these project contracts began in late 2007. Three patent applications also were filed (Appendix IV).

A few highlights of research accomplishments resulting from grants active in 2007 follow:

- At this time, limited therapeutic options are available for stemming the progression of evolving spinal cord injury or stimulating nervous system recovery once injury and disability have stabilized. The mandate of the Center for Research Excellence (CORE) in Spinal Cord Injury is to develop novel therapeutic approaches for evolving and stable injury. Work at the Burke/Cornell Medical Research Institute, under Rajiv Ratan, M.D., Ph.D., involves a multimodality approach that ultimately will combine drugs, cellular therapies and robotics. Toward this goal, four projects are underway at the CORE: (1) more than 50 drugs already used in humans have been identified and are being tested for use in spinal cord injury to discern the best agents for human clinical testing; (2) robots have been developed to enhance motor recovery of the upper and lower extremities of spinal-cord injured patients; (3) robots have been developed for rodent models to facilitate understanding of the biological targets activated in retraining the nervous system, and the dose and timing of these interventions; and (4) fundamental biology of glial and neural progenitor cells in human tissue is progressing systematically and rigorously. Computers have been leveraged optimally to advance experimental observations in the form of a state-of-the-art bioinformatics facility at Burke/Cornell Medical Research Institute.
- One of the major impediments to axonal regeneration after injury is inhibitors in myelin. Three myelin inhibitors have been identified: NogoA, MAG and OMgp. One approach to overcome these inhibitors and encourage regeneration is to change the intrinsic state of the axon so that it no longer recognizes these molecules as inhibitory. Using this approach, the laboratory of Marie Filbin, Ph.D., at Hunter College, City University of New York, showed that if neuronal cAMP levels are elevated, MAG and myelin in general no longer inhibit axonal growth. This cAMP effect is transcription-dependent, and four very different genes have been identified that are upregulated in response to elevation of cAMP. All four of these proteins block inhibition by myelin, and are being tested for their ability to promote regeneration *in vivo*. One of these upregulated proteins is the enzyme Arginase I (Arg I), key in the synthesis of polyamines. It was shown that the polyamine, putrescine, can block inhibition by both MAG and myelin in culture, and promote regeneration of central nervous system (CNS) axons after

injury. Furthermore, it was demonstrated that putrescine acts to overcome inhibition by activating the kinase CDK5, through upregulation of the CDK5 activator, p35. Another protein upregulated with cAMP is secretory leukocyte protease inhibitor (SLPI). SLPI overcomes inhibition by MAG and myelin in a dose-dependent manner. In addition, DRG neurons from animals that received SLPI intrathecally for 24 hours are also not inhibited by MAG and myelin when subsequently cultured. SLPI also promotes optic nerve regeneration when injected intraocularly at the same time as the optic nerve is crushed. Interestingly, SLPI enters the neuron and accumulates in the nucleus, which is necessary for it to overcome inhibition by MAG.

- In the laboratory of John Martin, Ph.D., at the College of Physicians and Surgeons, Columbia University, two complementary strategies to strengthen motor control signals caudal to the damaged spinal cord are being pursued to provide a bridge by which information can bypass the injury and to increase the number of spared connections. To achieve the first approach, a novel bridge was developed in the rat. A motor nerve originating from above the level of injury was cut from the muscle it innervates and inserted into the spinal cord below the injury. Motor axons in the bridge regenerated and synapsed on motor neurons and interneurons. Descending pathways can access this bridge circuit to evoke movements caudal to a spinal hemisection. Experiments are in progress to translate this approach to the cat – a large species in which axonal outgrowth must occur to a greater extent than in rodents to achieve meaningful results – and, if successful, then to the human. This strategy applies common spinal surgical techniques, and thus, could be readily used in humans. To increase spared connections after injury, activity-dependent processes were harnessed to promote corticospinal axon outgrowth. Using a rat model, a set of sparse corticospinal tract axons was targeted that remain after an injury, a condition similar to that of spinal injury patients. Electrical stimulation promotes outgrowth and, importantly, strengthens connections with spinal motor circuits. Ongoing studies in rats are examining whether these strengthened corticospinal tract connections improve motor skills. If so, this approach could be translated to humans using transcranial magnetic stimulation to activate the corticospinal tract noninvasively. Combining strategies for promoting connectivity caudal to the injury and strengthening spared connections may lead to greater functional improvement than either approach alone.
- Monkeys, rats and humans can gradually increase or decrease the H-reflex or other spinal reflexes through an operant conditioning protocol. This conditioning requires the corticospinal tract, causes both spinal and supraspinal plasticity, and affects other motor skills. In spinal-cord injured rats, appropriate H-reflex conditioning can improve locomotion. In the laboratory of Xiang-Yang Chen, Ph.D., at the Wadsworth Center, New York State Department of Health, it was shown that thoracic 8-9 right lateral column transection causes a locomotor asymmetry. Upconditioning the right soleus H-reflex eliminates this asymmetry. In rats not upconditioned, the asymmetry persists. Persons with partial spinal

cord injuries are also capable of spinal reflex conditioning, and a protocol to do this has been developed and validated in humans. In this work, three one-hour conditioning sessions per week over eight weeks gradually increased (upconditioning mode) or decreased (downconditioning mode) the soleus H-reflex. The results suggest that these changes involve plasticity such as that produced by reflex conditioning in animals. Furthermore, the reflex changes persist for months after conditioning ends. A study is now underway to determine whether H-reflex conditioning can improve locomotion in persons with spinal cord injuries. The initial study population comprises individuals in whom a foot drop significantly impairs locomotion. It is hoped that the appropriate H-reflex conditioning can alleviate this problem so as to improve the speed and symmetry, and /or reduce the metabolic burden, of locomotion. Spinal reflex conditioning might become an important new strategy for improving function after partial spinal cord injury. Protocols could be designed to address each person's deficit, and could complement other methods such as treadmill training. Reflex conditioning might be especially valuable once regeneration becomes possible, and precise methods for re-educating the regenerated spinal cord are needed.

The Board appreciates the opportunity to serve the citizens of New York State by focusing on such an important public health problem, and anticipates continued progress and success in achieving its mandates.

# Table of Contents

I.	Introduction.....	1
II.	Board Organization and Membership.....	2
	A. Spinal Cord Injury Research Board Members (as of December 31, 2007) .....	2
	B. Board Membership Changes in 2007.....	6
III.	Major Activities of the Board .....	6
	A. Meeting Schedule.....	6
	B. Bylaws.....	7
	C. Renaming the Center of Research Excellence .....	7
	D. Institute of Medicine Report .....	7
	E. 2006 Spinal Cord Injury Research Board Annual Report .....	8
	F. Presentation to the Board .....	8
IV.	Granting Activities for Research in Spinal Cord Injury .....	8
	A. RFA for Postdoctoral Fellowships, Mentored Research Scientist Development Awards and Mentored Clinical Scientist Development Awards .....	8
	B. CART/IDEA RFA .....	9
	C. CART, IDEA, Postdoctoral Fellowship and Mentored Scientist RFA.....	10
	D. Program Project RFA.....	11
V.	Research Accomplishments Associated With Existing Awards.....	12
VI.	Publications Resulting from SCIRB-Funded Research .....	36
VII.	Program Operations .....	37
VIII.	Fiscal Status of the Spinal Cord Injury Research Trust Fund.....	37
	Appendix I Legislation .....	38
	Appendix II Bylaws .....	41
	Appendix III 2007 Publications .....	47
	Appendix IV 2007 Patents .....	50
	Appendix V Presentation to the Board.....	52

**STATE OF NEW YORK**  
**SPINAL CORD INJURY RESEARCH BOARD**  
**2007 ANNUAL REPORT**

**I. Introduction**

The Spinal Cord Injury Research Board and the Spinal Cord Injury Research Trust Fund were authorized by legislation signed in July 1998, 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 VI of the State Finance Law. A technical amendment to the provisions of the State Finance Law was enacted in December 1999, under Chapter 612 of the Laws of 1999. The Board's enabling legislation is found in Appendix I to this document.

The Board's major responsibilities are:

1. To develop general policies and procedures for soliciting and selecting meritorious proposals to be recommended for funding to the Commissioner of Health. To meet this responsibility, the Board must undertake the following tasks:
  - a. Develop grant mechanisms and establish award amounts to:
    - stimulate creativity in the investigation of spinal cord injury (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.
  - b. Identify research areas of emphasis to:
    - address existing knowledge gaps or under-explored topics; and
    - ultimately find a cure for SCI.
  - c. Establish objective merit and programmatic review processes to:
    - identify projects with the greatest potential to impact SCI and its effects positively; and
    - foster the entry of new neurologic and neuroscience investigators into areas or disciplines with potential to reverse the consequences of SCI.
2. To report annually to the Governor and the Legislature on the oversight of the Spinal Cord Injury Research Trust Fund and the progress of Board-sponsored research programs.

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

## **II. Board Organization and Membership**

The Board is comprised of 13 appointed members, whose names, affiliations and brief biographies follow. The composition of the Board's membership is approximately one-third basic science researchers, one-third clinicians and surgeons, and one-third spinal cord-injured persons. Members serve four-year terms. Two Board seats are vacant. The Department of Health liaison and Executive Secretary to the Board is Bonnie Jo Brautigam.

### **A. Spinal Cord Injury Research Board Members (as of December 31, 2007)**

**Lorne Mendell, Ph.D.**, State University of New York at Stony Brook; **SCIRB Chair**

Dr. Mendell is a Distinguished Professor at SUNY-Stony Brook, and his laboratory focuses on the functional effects of neurotrophins in pain and segmental reflex pathways. Specifically, his research centers on the physiology of neurotrophins, and their action in modifying well-delineated circuits in the intact and injured spinal cord, including sensory input and motor output. His group is investigating the effects of neurotrophins on nociceptors and nociception in rats. In previous work, the team determined that administration of the neurotrophin nerve growth factor (NGF), known to be normally upregulated in skin during inflammation, produces hyperalgesia, and now is studying the basis for the peripheral component of this hyperalgesia. Another focus in his research is the action of neurotrophins such as NT-3 and BDNF on spinal reflexes and pathways in the neonatal rat. Dr. Mendell is the author of numerous journal articles and a past president of the Society of Neuroscience.

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

Dr. Carl came to Albany after medical training at the State University of New York (SUNY) at Buffalo, post-graduate experience in orthopedics at New York University-Bellevue Hospital in New York City and spine injury training at the University of Toronto. He has been 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 area of interest, as he perceived it as one of 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 the Capital District, he has collaborated with Rensselaer Polytechnic Institute, the General Electric Company and the State University of New York at Albany. 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 for the past six years, spinal cord injury 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.

**Brooke M. Ellison, M.A.,** Founder and President of The Brooke Ellison Project

Brooke Ellison has worked as an advocate for stem cell research for nearly a decade. 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 let her physical condition 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 movie directed by Christopher Reeve. For more than a decade, Brooke has worked across 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. In 2006, Brooke ran as a candidate for the New York State Senate, focusing on the need for New York State to commit funding to stem cell research. Brooke has continued her work in the field of stem cell research, and in July 2007 formed a non-profit organization, *The Brooke Ellison Project*, to educate and mobilize the public on behalf of stem cell research. Moreover, working with leading scientists and advocates in the field, Brooke is now working on a documentary to disseminate the necessary information to advance stem cell research.

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

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 of both the regulation and plasticity of synaptic transmission, the role of intrinsic membrane properties in both normal and abnormal operation of neural networks, as well as the physiological consequences of nerve cell responses to injury.

Dr. Faber earned his 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 and at the Hospital Salpêtrière in Paris, before returning to the U.S. to join the faculty of the University of Cincinnati in 1972. He moved to the Department of Physiology at Buffalo in 1974, where he was named an associate professor and director, Division of Neurobiology in 1978 and rose to professor in 1981. In 1992, he moved to MCP-Hahnemann School of Medicine as chair of the Department of Neurobiology and Anatomy and a member of the School's Spinal Cord Injury Program, until he moved to Albert Einstein in 1999. Dr. Faber has served as a consultant to the National Institutes of Health (NIH) and the National Science Foundation (NSF), as well as on the editorial boards of three major journals. His extensive professional recognition includes 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.

**Deborah A. Hrustich, M.D.**, Albany-Troy Neurosurgical Associates, P.C.

In addition to serving as a neurosurgeon at Albany-Troy Neurosurgical Associates, Dr. Hrustich holds concurrent medical staff appointments in the Capital District at Albany Medical Center, St. Peter's Hospital, Albany Memorial Hospital, St. Mary's Hospital and Samaritan Hospital. She is a member of several medical societies such as the New York State Medical Society, the New York State Society of Surgeons, and the American Medical Association.

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

Dr. Huang is assistant professor of neurosurgery at the University of Rochester Medical Center and attending neurosurgeon at Strong Memorial Hospital and Unity Hospital at Rochester, where he directs the neurotrauma and peripheral nerve surgery programs. He is author or co-author of 75 peer-reviewed papers, abstracts, editorial reviews and book chapters. Dr. Huang earned his medical degree in 1999 from Johns Hopkins University School of Medicine. In 1994, he received a bachelor of arts degree, *magna cum laude*, in the neurosciences from Amherst College. Dr. Huang underwent his 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 is also a major in the United States Army Reserves and was recently deployed to Iraq to treat injured soldiers with brain and spinal trauma for Operation Iraq Freedom.

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

Dr. Koppel is chief of neurology at Metropolitan Hospital 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. Dr. Koppel is the author of numerous journal articles, book chapters and abstracts.

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

Dr. Paige received his undergraduate education in 1970 at the University of California at Irvine in biological sciences. He then moved to the University of Chicago's Medical Scientist Training Program, where he completed medical school (M.D., 1980) and graduate training in physiological and pharmacological sciences (Ph.D., 1981) on vestibular neurophysiology with Jay M. Goldberg. He followed with an internship at Michael Reese Hospital in Chicago and an ophthalmology residency at the University of California at San Francisco in 1985. Dr. Paige then joined the faculty of Washington University in 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 in the 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 Kilian J. and Caroline F. Schmitt Professor and chair of the Neurobiology and Anatomy Department at the University of Rochester Medical Center, while concurrently holding joint appointments in the Medical Center's Departments of Neurology, Ophthalmology, Biomedical Engineering, and Brain and Cognitive Science.

Dr. Paige's research on multisensory interactions underlying spatial orientation focuses on how the brain integrates visual and auditory sensory inputs from the outside world with the internal senses (vestibular and somatosensory) to depict accurately humans' orientation, motion and behavior. Equally important to this topic is 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, his academic activities include various levels of medical and graduate instruction. Peer review assignments include NIH (and other) panels, as well as a range of journal review responsibilities and editorial duties. Dr. Paige has served on the governing boards of professional organizations, among others, as president of the Association of Medical School Neuroscience Department Chairs and vice president of the Society for the Neural Control of Movement.

**Paul Richter, Spinal Cord Society**

Mr. Richter is responsible for the 1998 legislation that created the Spinal Cord Injury Research Board. He was serving as a State Trooper Zone Sergeant 34 years ago when he was shot three times and was left with a spinal cord injury.

**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 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 16 years and School Attorney for the Webutuck (New York) Central School District for three years. He became interested in finding a cure for spinal cord injury after his son, David, was paralyzed from the neck down as the result of a motorcycle accident.

**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 for 25 years. 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 a

fellowship in neurophysiological research at the NIH. He is chief of Wadsworth's Laboratory of Nervous System Disorders and a professor in the Department of Biomedical Sciences, SUNY University at Albany's School of Public Health. 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. These methods are now being applied to the study of spinal cord injury and to development of new treatment methods. Dr. Wolpaw is also designing electroencephalograph-based brain-computer interface technology as a new communication and control channel for those with severe motor disabilities. He is the author of numerous journal articles and holds several NIH grants.

## **B. Board Membership Changes in 2007**

The following Board members resigned during this reporting period:

- David Carmel, New York Stem Cell Foundation and Alliance for Stem Cell Research
- David Whalen, Esq., New York State Office of Court Administration

## **III. Major Activities of the Board**

### **A. Meeting Schedule**

The Board is mandated to meet twice per calendar year, yet three Board meetings were held during 2007.

A Board meeting was convened on January 25, 2007 at the Wadsworth Center's David Axelrod Institute, New Scotland Avenue, Albany, with a videoconference site at Cicatelli Associates, Inc., 505 Eighth Avenue, New York City. No members of the public requested to speak at the meeting.

On April 19, 2007, another Board meeting was held at the same locations in Albany and New York City. During the public comment period, one member of the public identified a need to update the Department of Health's website to facilitate access to information, and recommended that the State's laws be amended to enable collaboration with the private sector on development of new human SCI treatments and evaluation. It was emphasized that research needs to progress more rapidly to realize timely treatment results.

On June 29, 2007, a third Board meeting was organized at the Wadsworth Center's David Axelrod Institute, with a videoconference site at the Department of Health's Metropolitan Regional Office, 90 Church Street, New York City. No members of the public were present at the meeting.

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

## **B. Bylaws**

No changes were made to the bylaws in 2007. The bylaws are found in Appendix II.

## **C. Renaming the Center of Research Excellence**

In August 2003, the New York State Department of Health guided the formation of the Center of Research Excellence (CORE) in Spinal Cord Injury. In 2005, the Board voted to rename the CORE, first for Christopher Reeve, and then for Paul Richter. The Commissioner of Health approved both actions in 2006. Appropriate legal actions are being taken to rename the CORE after these distinguished contributors to the Board's mission.

## **D. Institute of Medicine Report**

The following excerpt is taken from the SCIRB-commissioned Institute of Medicine (IOM)'s 2005 report, "Spinal Cord Injury: Progress, Promise, and Priorities":

An estimated 11,000 spinal cord injuries occur each year in the United States, and 247,000 Americans are currently living with a spinal cord injury. The newly discovered potential for central nervous system (CNS) regeneration and repair has opened up numerous therapeutic targets and opportunities. Many current avenues of research suggest that a concerted research effort on spinal cord injuries could result in important gains in restoring function and improving quality of life.

Recognizing this wealth of new opportunity, the New York State Spinal Cord Injury Research Board asked the Institute of Medicine (IOM) to examine future research directions in spinal cord injury. The IOM was asked not just to advise New York State on its research program, but to look more broadly at research priorities for funders of spinal cord research, including federal and state agencies, academic organizations, pharmaceutical and device companies, and nonprofit organizations. To accomplish this task, the IOM appointed a 13-member committee with expertise in basic and clinical neuroscience research, trauma surgery, health care, biomedical engineering, clinical research methods and research management.

This report by the IOM Committee on Spinal Cord Injury provides a broad overview of the current status of spinal cord injury research, examines the research and infrastructure needs, and provides recommendations for advancing and accelerating progress in the treatment of spinal cord injuries, with particular attention to issues regarding translational research.

The committee also addresses the contributions that the New York State program can make to complement the scientific efforts of other state, federal and private supporters of research in this area.

During 2007, the Board voted to rescind the action plan it had adopted following issuance of the IOM Report. In lieu of embracing a new action plan, the Board noted that Program staff will continue to consider the IOM report and recommendations in proposing future actions for Board consideration.

#### **E. 2006 Spinal Cord Injury Research Board Annual Report**

At its April 19, 2007 meeting, the Board approved the 2006 Annual Report, including a summary of funded researchers' accomplishments.

The 2006 Annual Report, setting forth the status of funds appropriated for spinal cord injury research and the progress reflected in the results of Board-funded spinal cord injury research efforts, has been distributed to the Governor and leaders of the State Senate and Assembly.

#### **F. Presentation to the Board**

On January 25, 2007, Dr. Rajiv Ratan, director of the SCIRB-funded Center of Research Excellence, gave a presentation, "Update on the CORE: Progress Toward a Search for a Cure for Evolving and Stable SCI." Dr. Ratan distributed a copy of the presentation, as well as CORE-generated articles entitled, "Novel Robotic Technology for the Spinal Cord Injury Center," and, "Astrocytes Derived From Glial-Restricted Precursors Promote Spinal Cord Repair." Slides from that presentation appear here as Appendix V.

### **IV. Granting Activities for Research in Spinal Cord Injury**

#### **A. RFA for Postdoctoral Fellowships, Mentored Research Scientist Development Awards and Mentored Clinical Scientist Development Awards**

On November 30, 2005, the Spinal Cord Injury Research Board issued an RFA for Postdoctoral Fellowships, Mentored Research Scientist Development Awards and Mentored Clinical Scientist Development Awards. Thirteen applications were received, and 11 were recommended for funding by SCIRB, with contract start dates of April 1, 2007. The Board expects that outcomes of supported activities will considerably benefit future SCI research and/or education efforts. To fulfill this vision, applications may address any topic or issue related to spinal cord injury, with any investigative approach appropriate to the application topic.

Of the 11 recommended applications, seven were awarded Postdoctoral Fellowships. The intent of the Postdoctoral Fellowship Awards is to support continued training of basic or clinical investigators with exceptional potential for making significant

contributions to cures of SCI and SCI-induced paralysis. The awards are for a two-year period. The objective of the Mentored Research and Clinical Scientist Development Awards is to underwrite the transition of neuroscientists and neurologists into spinal cord injury research careers at New York institutions. The awards are for a three-year period.

Four of the awards were for Mentored Research Scientists. The Mentored Research Scientist Development Award (K01-like award) funds an intensive, supervised career development experience in one of the biomedical, behavioral or clinical sciences, leading to independent research support. The candidate must be able to demonstrate the need for a three-year span of supervised research, as well as the capacity and/or potential for highly productive independent research. The proposed career development experience must be in a research area new to the applicant and/or one in which extended supervised research training will add substantially to the research capabilities of the applicant. The candidate must provide a plan for attaining independent research support by the end of the award period.

The RFA did not result in awards for Mentored Clinical Scientist Development. The award provides support for development of outstanding clinical research scientists. This mechanism funds specialized study for individuals with a health professional doctoral degree committed to a career in laboratory or clinical research. Candidates must have the potential to develop into independent investigators. The award supports a three-year period of supervised research experience that may integrate didactic studies with laboratory- or clinically-based research. The proposal must hold intrinsic research merit, as well as serving as a suitable vehicle for learning the methodology, theories and conceptualizations necessary to become a well-trained independent researcher.

## **B. CART/IDEA RFA**

On November 30, 2005, the Spinal Cord Injury Research Board issued an RFA for Collaborations to Accelerate Research Translation (CART) and Innovative, Developmental or Exploratory Activities (IDEA) Awards. Twenty-four applications were received, and 11 were recommended by SCIRB for approval, with contract start dates of April 1, 2007.

The goal of the CART funding mechanism is to foster translation of results from basic (preclinical) research into the next research phase by supporting synergistic partnerships in/among various scientific disciplines and/or organizations. This mechanism is expected to contribute to more rapid translation of basic science findings to potential therapeutic applications or clinical research through novel or innovative treatment strategies.

The collaborative partnerships must facilitate expansion of the body of knowledge/expertise applied to research problems in spinal cord injury. The CART mechanism is expected to encourage experts from other fields to bring their knowledge to bear on problems in spinal cord injury research. Supporting interactions and cooperation, and facilitating cross-disciplinary research are anticipated to lead to creative solutions to previously intractable problems in spinal cord injury treatment.

The intent of the Innovative, Developmental or Exploratory Activities (IDEA) Awards is to fund novel scientific approaches to spinal cord injury research that, although as yet untested, promise a significant likelihood of resulting in breakthroughs or new avenues of investigation. Researchers are also encouraged to explore new concepts, to challenge existing paradigms or to address overlooked gaps in knowledge.

The IDEA research grant allows established researchers to enter the spinal cord injury field and affords researchers the opportunity to try new methods and approaches to investigate the problems of spinal cord injury, e.g., implantable nanobiotechnological devices to create new neuromotor replacements for nerves damaged by spinal cord injury.

Upon project completion, the principal investigator should have: 1) opened a new area of investigation; 2) satisfactorily tested a novel or innovative hypothesis; and/or 3) produced viable data for preparation of a full-scale research application to the SCIRB Program or another funding agency. It is the intent of the Board that successful IDEA project PIs also be eligible to apply for CART awards.

### **C. CART, IDEA, Postdoctoral Fellowship and Mentored Scientist RFA**

On October 31, 2007, the Spinal Cord Injury Research Board issued an RFA to solicit applications for CART, IDEA, Postdoctoral Fellowship, Mentored Research Scientist Development and Mentored Clinical Scientist Development Awards.

This RFA supports the same funding mechanisms offered through the 2007 grant awards. Combining these grants into one RFA is intended to streamline the award process and help expedite the critical funding needed to promote and expand SCI research.

Applications for this RFA were due January 2, 2008, with SCIRB recommendations for awards scheduled to occur at the next regular business meeting of the Board. The estimated start date of the contracts awarded through this RFA is October 1, 2008. The duration and funding of the contracts will depend on the funding mechanism, as follows:

- CART - duration of four years; annual direct costs are capped at \$300,000
- IDEA - duration of two years; annual direct costs are capped at \$150,000
- Postdoctoral Fellowship - duration of two years; stipend plus annual direct costs; annual direct costs in excess of stipend are capped at \$20,000
- Mentored Research Scientist Development - duration of three years; annual direct costs are capped at \$200,000

- Mentored Clinical Scientist Development - duration of three years; annual direct costs are capped at \$200,000

It is the intent of SCIRB to issue this RFA on a yearly basis beginning in May 2008.

#### **D. Program Project RFA**

On November 7, 2007, the Spinal Cord Injury Research Board issued a Program Project RFA. The Program Project mechanism is designed to support research for which the funding of several interdependent projects offers significant scientific advantages over support of these same projects as individual research grants. The Program Project can facilitate support of essential shared core facilities, e.g., major equipment; however, the need of a group of investigators for a major piece of equipment or a core facility does not in itself justify a Program Project grant. Administrative cores are not fundable, but limited administrative support for the project is acceptable. Further, it is expected that successful Program Projects will establish effective collaborations, particularly in emerging areas of research, that extend beyond the life of the Program Project grant itself.

A Program Project usually consists of three to five individual interdependent projects headed by different investigators. This interdependence is designed to advance the field farther than independent conduct of each project. The scientist designated by the applicant institution as the principal investigator is responsible for the overall scientific leadership and fiscal management of the award. It is expected that each of the collaborating scientists charged with the individual projects will be independent investigators. Investigators from more than one department, administrative unit or institution (through a subcontract mechanism) are commonly included. The program project is not intended to be a vehicle for departmental support, nor is the research support of a single senior investigator and several postdoctoral and research associate-level scientists appropriate under this mechanism. Also, the program project and each individual project must represent a significant effort on the part of the participating scientists and remain discrete from their other funded efforts.

Applications for this RFA were due March 14, 2008, with SCIRB recommendations for awards scheduled for the July 2008 regular business meeting of the Board. The estimated start date of the Program Project contracts is January 1, 2009, with a duration of five years, and annual direct costs capped at \$1 million.

It is the intent of SCIRB to issue this RFA on a biennial basis in January, with a contract start date of the following January.

## V. Research Accomplishments Associated With Existing Awards

Previously unreported highlights of research accomplishments related to 52 active SCIRB grant contracts follow:

- **Roman Giger, Ph.D., University of Rochester, “Promoting Neuronal Repair: Attacking Myelin by Phage Display,” October 1, 2001 – September 30, 2007 CART award.**

Spinal cord injury (SCI) occurs when a traumatic event damages cells within the spinal cord or severs the nerve tracts that relay signals up and down the spinal cord. While recent advances in emergency care and rehabilitation allow many SCI patients to survive, methods for reducing the extent of injury or for restoring lost function are still extremely limited. Following SCI, regenerative growth of injured nerve cells is blocked, at least in part, by potent inhibitors of growth associated with spinal cord white matter tissue. The inability of injured nerve cells to regenerate spontaneously following SCI leads to permanent neurological deficits. A detailed understanding of the molecular players that impair regenerative growth in the injured spinal cord is key to rational design of strategies aimed at promoting repair after SCI. Over the past years, several proteins that inhibit growth of nerve cells have been identified and characterized. One successful approach to promote functional recovery of SCI in animal models is neutralization of growth-inhibitory proteins with antibodies. Use of specific antibodies to neutralize inhibitors of growth following SCI leads to significant functional improvements. Antibody-based therapies to repair SCI are primarily confined to experimental animal models of SCI for several reasons. First, only a limited number of growth-inhibitory proteins and their mechanisms of action have been defined thus far. This gap in knowledge greatly limits the ability to target and neutralize effectively the majority of molecular players that inhibit nerve cell repair following SCI. Second, very few antibodies directed against proteins that inhibit growth are now available, and importantly, antibodies must block the activity of inhibitors and be engineered for humans to be useful for clinical trials. With research funds provided by the NYS Department of Health, new proteins were identified that participate in growth-inhibitory signaling cascades in the injured spinal cord. Antibodies were also raised against two proteins important for signaling growth-inhibitory responses to neurons. A technology, phage display, that generates antibodies readily channeled into human clinical trials, has been employed. This work has resulted in several publications in peer-reviewed journals and scientific presentations at international conferences on spinal cord injury repair.

- **Maiken Nedergaard, M.D., Ph.D., University of Rochester, “Purinergic Signaling in Spinal Cord Injury,” November 1, 2003 – October 31, 2007 CART award.**

Delayed injury, which typically develops as tissue surrounding the initial injury site, gradually expands and is incorporated into the original lesion. In experimental stroke and head trauma models, a phenomenon named spreading depression has been shown to

contribute very significantly to secondary injury, as each wave of spreading depression is linked to a 23-percent expansion of the infarct volume. Little is known about similar processes in SCI. It has been demonstrated that spinal cord injury is associated with transmitter adenosine triphosphate (ATP), which activates cell signaling by binding to membrane receptors, specifically, the purinergic receptor. Preliminary observations here have shown that acute spinal cord injury is characterized by abnormal increases in ATP release in the areas surrounding the traumatic lesion. Since both neurons and oligodendrocytes express purinergic receptors resulting in cellular degeneration, this study tests the hypothesis that abnormal purinergic signaling events trigger additional and delayed injury in the spinal cord after injury. Preliminary observations indicated that animals that received treatment with a purinergic receptor antagonist, suramin, recovered significantly better than untreated animals in an experimental spinal cord injury model. By combining single-channel recordings with bioluminescence imaging of ATP, it was found that connexin (Cx) hemichannels are activated in response to depolarization, and the opening of hemichannels is linked to excessive ATP release.

Spinal cord motor neurons express P2X7 receptors and high ATP levels outside the cells at the site of spinal cord injury, causing excitotoxic neuronal death. An antagonist of P2X7 receptor, OxATP, reduced injury at the cell level and improved functional recovery. Findings here showed that ATP and ATP agonists potently trigger Ca<sup>2+</sup> increases in both spinal cord neurons and oligodendrocytes. Experiments are underway to define the purinergic receptors that mediate the Ca<sup>2+</sup> increases in spinal cord neurons and oligodendrocytes.

- **Marie Filbin, Ph.D., Hunter College, City University of New York, “Overcoming Myelin Inhibitors to Promote Regeneration *in vivo*,” November 1, 2003 – October 31, 2007 CART award.**

Nerves of the adult spinal cord do not spontaneously regrow after injury. This is due largely to the presence of molecules that actively inhibit regeneration. One such molecule, MAG, is found in the myelin membrane that insulates nerves. It has been shown that with an increase in the amount of cAMP, an agent found in all cells of the body, nerves are no longer inhibited by MAG or myelin. One strategy to increase the level of cAMP is to block its degradation. A drug available for other diseases, rolipram, inhibits the degradation of cAMP. Here, rat studies have shown that upon spinal cord injury, if implanted with embryonic tissue into the injury site at the time of injury, with rolipram delivered two weeks later, the rats recovered lost function. In addition, nerve regeneration was observed, and the formation of scar tissue was less severe than in rats not receiving rolipram. It was also found that delivery of rolipram alone, without implanted embryonic tissue, results in sprouting of nerves above the site of injury. This sprouting appears to lead to an improvement in function.

It was also shown that for elevated cAMP to have an effect on nerve regeneration, it must trigger the synthesis of new proteins. One protein that increases as a consequence of cAMP elevation is IL-6. It has now been demonstrated that IL-6 can induce nerves to

grow through the inhibitors MAG and myelin, and can encourage nerve regeneration in the rat spinal cord. Unfortunately, IL-6 also induces an increased inflammatory response that can cause additional damage in the nervous system and so is unlikely to be suitable for treatment in humans.

- **Zaven Kaprielian, Ph.D., Albert Einstein College of Medicine, “Regulating Axon Guidance in the Vertebrate Spinal Cord,” November 1, 2003 – October 31, 2007 CART award.**

Proper development of a functioning spinal cord requires that the leading edge of a given axon navigate over long distances to find its correct final target. During this process, axons must pass through specific intermediate targets to extend properly along the next leg of their journey. Commissural axons extend from one side of the spinal cord to the other (left to right or right to left) by passing through a midline structure known as the floor plate. After crossing through the floor plate, commissural axons are thought to lose their ability to respond to midline-associated positive guidance cues, which initially attract them to the floor plate, and gain responsiveness to midline-derived inhibitory signals, which ultimately drive them away from the floor plate and along new trajectories.

To study this process, a reproducible and reliable genetic labeling system was developed and characterized that makes it possible to visualize selectively subsets of commissural axons in the developing mouse and chick spinal cord. Employing specific sequences of regulatory DNA, expression of Robo1 or Robo2 on precrossing segments of commissural axons in chick/mouse embryos was prompted. Consistent with a key prediction of the central hypothesis underlying studies in this laboratory, it has been shown in the chick spinal cord that misexpression of Robo2 prevents particular classes of commissural axons from crossing through the floor plate. In a converse set of experiments, misexpression of truncated forms of Robo1 or Robo2, which are functionally inactive, was completed on one side of the spinal cord in chick embryos. This perturbation prevents essentially all commissural axons on either side of the spinal cord from leaving the ventral midline and projecting toward their final targets.

It is hoped that the established genetic labeling strategy could be used in conjunction with loss-of-function and gain-of-function approaches to investigate the *in vivo* roles of a variety of axon navigation systems within relatively homogeneous populations of commissural axons. Collectively, these studies represent the first *in vivo* tests of the so-called altered-responsiveness model of midline guidance, and present findings support the long-held, but previously unsubstantiated, view that upregulation of particular repellent guidance receptors on postcrossing segments of commissural axons facilitates expulsion of the axons away from the floor plate.

- **George Forrest, M.D., Albany Medical College, “Implanted Neuroprostheses for Exercise, Standing and Transfers,” November 1, 2003 – October 31, 2007 CART award.**

The purpose of this project is to develop a system of functional electric stimulation that will allow patients with spinal cord injury to stand and transfer. Successful implementation and proper use of such systems can greatly improve the quality of life of previously immobile patients, and may help alleviate confounding problems such as osteoporosis and cardiovascular disease. The components of the system in this study are: a radiofrequency transmitter that turns the system on and off; a receiver/stimulator implanted under the skin of the abdomen; and electrodes implanted in the paraspinal muscles at L1, the vastus lateralis, and semimembranosus and gluteus maximus muscles, bilaterally. The amplitude of stimulation is 20 milliamperes and the frequency is 20 hz. The pulse width varies from 70-200 microseconds, as needed, to elicit contraction of the muscle.

Two subjects have enrolled in the study. The first subject was a C7 ASIA B quadriplegic man, implanted with the functional electric stimulation system in October 2004. He has completed his training and is using the system frequently at home for exercise. He can transfer and stand independently for as long as two hours. He can walk 15 feet with a swing to the gait. The only complication was that the lead to his left gluteus maximus is not functioning. The investigators do not wish to replace this lead, as the lead to the left semimembranosus muscle elicits hip extension, and it is felt that the benefit from repairing the nonfunctioning lead warrants another operation. Metabolic testing showed that the energy demand of the subject using the system is two METS, comparable to a nondisabled person's walking at two miles per hour. The second subject is a T6 ASIA B paraplegic patient. His initial surgery was performed on May 13, 2005. The subject's training was interrupted in November 2005 when he was injured. The injury was not related to the device, but resulted in burns to the abdomen over the area of the implant, dislodging components of the receiver stimulator. By September 2006, the burns healed sufficiently for the subject to undergo an operation to replace the damaged receiver/stimulator. The patient tolerated the surgery, but in the course of his therapy, the lead to the right quadriceps muscle separated from the muscle. In June 2007, the subject underwent another operation to repair the right vastus lateralis lead and reposition the lead to the left vastus lateralis lead. The surgery proceeded without complication. The subject has used the system to exercise at home for several weeks and began transfer training again at physical therapy during September 2007.

Despite the small number of patients in the study, this technology is now available to residents of New York State wishing to enroll, and the capability to perform the surgery and provide necessary therapies is now available at Albany Medical Center. The first subject achieved the goals of independent transfers and standing with the system. The team expects the second subject to meet those goals as well. The effect of this technology on the cardiovascular system of the first subject was documented and published in a peer-reviewed journal. The data on bone density are being collected.

- **Giacinto Grieco, M.D., New York University, “Validity and Reliability of Spinal Cord Injury Assessments,” November 1, 2003 – April 30, 2007 IDEA award.**

The primary objective of this study was to develop methods for reliable and efficient assessment of potential treatments for acute spinal cord injury (ASCI) in future treatment trials. Neuroanatomically and neurophysiologically driven explorations and analyses of the study data were performed as proposed in the study plan. These were based on raw data (including six-grade manual muscle test [MMT] scores on individual muscles, and pinprick and touch sensory scores on individual dermatomes) from all study visits and on calculated values, including:

- summed MMT scores (for individual limbs, upper limbs combined, lower limbs combined and all limbs combined);
- MMT scores rescaled and analyzed as three ordinal categories;
- summed sensory scores;
- algorithmically determined unilateral (right and left side), and bilateral relative and absolute levels of sensory (light touch and pinprick) and motor impairment;
- changes from study baseline in individual and summed MMT scores;
- changes from study baseline summed sensory scores;
- coefficients of changes in summed MMT and sensory scores; and
- changes from baseline in relative and absolute neurologic levels of motor and sensory impairment.

Changes from baseline were analyzed for each study visit separately and throughout all study visits by appropriate techniques (e.g., repeated measures MANOVA for continuous outcome measures).

Based on these analyses, it was concluded:

- The baseline neurologic level of absolute impairment in pin sensation (the highest dermatomal level, so that there is no pin sensation at or below that level on either side of the body), treated as a categorical variable, is the baseline clinical measurement with the strongest positive predictive value for improvement in all unidimensional measures of motor and sensory outcomes directly derived from clinical examination. No other baseline variable is predictive of as many outcome measures.
- All outcome measures are flawed, clinically and statistically.
- Multi-dimensional measures (e.g., ASIA Impairment Score) are more problematic than unidimensional measures (e.g., sensory scores, motor levels of impairment).
- No one outcome measure adequately describes change in neurologic function among ASCI patients over time.
- Correlations among different outcome measures are highly variable.

- Even whenever two outcome measures are strongly correlated, many subjects exhibit highly inconsistent changes in those measures.

For future treatment trials, it is recommended that:

- multiple unidimensional primary outcome measures be used;
  - each primary outcome measure directly assess spinal-cord mediated function by means anatomically and physiologically relevant to ASCI (e.g., improvement in upper extremity strength is not an appropriate primary measure for subjects with mid-thoracic cord injury);
  - the primary outcomes include assessments of motor and sensory levels of impairment, upper extremity motor function separately from lower extremity function, and sensory function;
  - multidimensional measures not be used as primary outcomes;
  - treatment success be defined as a composite outcome (e.g., statistically significant improvement in at least two primary measures, with no trend to deterioration in any primary measure);
  - the absolute level of pin sensory loss be analyzed as a baseline predictor value (independent variable for all primary outcomes); and
  - other variables be analyzed, as appropriate, for each primary outcome.
- **Rajiv Ratan, M.D., Ph.D., Burke/Cornell Medical Research Institute, “A Novel Multimodality Approach to Treating Spinal Cord Injury,” May 1, 2004 – April 30, 2009 Center of Research Excellence award.**

Spinal cord injury is a prevalent and visible cause of disability in the United States. At present, limited therapeutic options are available for stemming the progression of evolving spinal cord injury or stimulating nervous system recovery once injury and disability have stabilized. The overriding, urgent mandate of the Center for Research Excellence (CORE) in Spinal Cord Injury is to develop novel therapeutic approaches to evolving and stable injury. The efforts of the Center involve a multimodality approach ultimately to combine drugs, cellular therapies and robotics. Toward this goal, drug screening, progenitor biology, and development of animal and human robotic prototypes have been undertaken within CORE during the first 30 months of its existence. Drugs already used in humans have been identified (cyclopirox, daidzein) and are showing significant promise in rodent models of spinal cord injury. The agents tested to date constitute only a fraction of the novel compounds identified within CORE, and throughput and interactions are being quickly ramped up to discern the best agents for human clinical testing among the more than 50 new candidate drugs found. Interactions also have been facilitated within CORE between MIT, UCSF and Burke/Cornell that have accelerated the development of robots to enhance motor recovery of the upper and lower extremities of spinal-cord injured patients. Novel development has also intensified in the area of robots for rodents with experimentally induced spinal cord injuries. Rodent robots will facilitate understanding of the biological targets activated to retrain the nervous system, and the dose and timing of these interventions. Fundamental biology of

glial and neural progenitor cells in human tissue is being advanced systematically and rigorously. Computers have been leveraged optimally to accelerate experimental observations in the form of a state-of-the-art bioinformatics facility at Burke. Regular meetings and informal interactions have increased the synergies developing within CORE.

- **Sally Temple, Ph.D., Albany Medical College, “Engineering Embryonic Spinal Cord Stem Cells for Spinal Cord Injury Repair,” January 1, 2006 – December 31, 2009 CART award.**

Spinal cord injury (SCI) is a complex problem, and researchers have found that therapies involving multiple interventions are likely to be most beneficial. Previous research here has produced a novel type of stem cell as yet untested for SCI - Esco cells, which are derived from embryonic spinal cord. Esco cells efficiently produce many types of spinal cord neurons, including motor neurons, and glia such as oligodendrocytes, which are known to be beneficial for SCI. Therefore, it is important to establish Esco cells' utility for SCI. Previous studies have shown that implanted stem cells in the SCI zone do not have access to growth factors needed for efficient development into useful spinal cord cells. In collaboration with Dr. Ravi Kane, a chemical engineer specializing in design of biomaterials for long-term delivery of factors to stem cells *in vivo*, the goal of this project is to direct implanted stem cells to develop as useful spinal cord cells.

To date, the laboratory has generated Esco cells engineered to produce the growth factor IGF-1 and found that IGFI overexpression resulted in a significant increase in neuron production by Esco cells and a decrease in cell death and IGFI-overexpressing Esco cells promoted the outgrowth of corticospinal axons. After implanting the normal Esco cells and the IGF-1 secreting Esco cells into SCI mice, it was determined that mice receiving cells overexpressing IGFI showed behavioral improvements in hind-limb mobility. Furthermore, IGFI-overexpressing Esco cells generated fewer astrocytes than control Esco cells beneficial for recovery from SCI.

Biodegradable microspheres releasing chondroitinase, an enzyme that can disintegrate scar tissue forming at the injury site, were developed and tested in the mouse SCI model. It was found that transplantation of chondroitinase-releasing beads resulted in significant behavioral recovery of mice. The next step is to use microbeads releasing Shh, a growth factor that can direct stem cells towards useful cell types for SCI recovery.

- **Christopher Henderson, Ph.D., Columbia University, “Screening for Small Molecules With Activity in CNS Regeneration,” January 1, 2006 – December 31, 2009 CART award.**

One of the major hurdles preventing regeneration following spinal cord injury is the very slow spontaneous regrowth of injured nerve fibers, called axons, in the hostile environment of the damaged adult nervous system. Different approaches are being

undertaken to overcome this obstacle, including attempts to block the inhibitory molecules expressed by other cells in the spinal cord. This study takes a complementary approach: attempting to identify chemical compounds for boosting the ability of neurons to send out axons, even in the presence of inhibitory molecules. This strategy is a collaboration among three laboratories: 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 for high-throughput screening of chemical libraries with tens of thousands of compounds for their ability to trigger axonal regeneration in the culture dish. The overall objective of the project is to identify chemical compounds that affect axonal growth under these conditions. Many of the compounds should offer new insights into the molecular mechanisms underlying regeneration. A smaller number, perhaps one or two, should have properties that position them for further development as drug candidates.

Year One of the project was aimed at defining conditions and protocols for running an industry-standard assay in collaboration with the three New York City academic laboratories. This endeavor has been highly successful. The system selected to move forward with screening involves spinal motor neurons derived from embryonic stem cells. This strategy provides an abundant and reproducible source of neurons that are highly relevant to regeneration of motor function. These cells are grown on a monolayer of fibroblasts engineered to express the growth inhibitor MAG at their surface. Axons from the motor neurons encounter MAG and, therefore, refuse to grow unless given compounds such as cyclic AMP, which can stimulate the axons and serves as a positive control in the screen. Other compounds are tested one-by-one in an automated manner for their ability to perform as well as, or better than, cyclic AMP. As a pilot screen to validate the assay, 2,000 known drugs are undergoing testing. During the next three years, a large number of compounds will be screened, and identified “hits” will be tested in other neuronal assays and in animal models of spinal cord injury.

- **John Martin, Ph.D., “Bypassing Spinal Cord Injury to Promote Motor Function,” January 1, 2006 – December 31, 2009 CART award.**

Spinal cord injury (SCI) interrupts connections between the brain and spinal cord transmitting motor control signals and somatic sensory messages, but typically leaves the spinal circuits below the lesion intact. This project aims to develop a bridge for these connections around a spinal cord injury in the cat, based on studies here in the rat. Success in the cat is the transition towards translating this bridging approach to human patients with spinal cord injury.

After developing the cat spinal bridge model and a consistent surgical model, the tracing method devised for the rat was extended to the cat. Four of six cats showed bridge nerve outgrowth, including one in which bridge nerve stimulation evoked hind leg muscle contraction and movement. While encouraging, the level of outgrowth in the cats, compared with the rat, is consistently much lower. This finding led to a plan to determine whether growth is enhanced when the nerve bridge is inserted caudal to a

spinal lesion. In methodological experiments on the rat, it was found that insertion of the bridge nerve caudal to a spinal hemisection resulted in regeneration of stronger connections. As a consequence of this finding, it is important to shift focus in the cat from characterizing bridge nerve outgrowth in the intact cord to the cord caudal to a spinal injury.

Anticipating further outgrowth and optimization, methodological experiments have been conducted in rats to develop a suitable means of recording from and stimulating the bridge nerve noninvasively and to design an efficient method for activating the bridge circuit using rostral spinal stimulation. Future efforts will focus on conducting immunocytochemistry on regenerating axon terminals to determine the nature of the synaptic connections, characterize changes in bridge motoneurons associated with axon regeneration and synaptogenesis, and begin conducting electrophysiology experiments.

- **Jane Lin, Ph.D., New York Medical College, “Bystander Death in Traumatic Spinal Cord Injury,” January 1, 2006 – December 31, 2009 CART award.**

The extent of spinal cord injury may be critically dependent on the balance between propagation of “death” signals and the resistance these signals evoke in cells. Cells in victims of spinal cord injury may not need to receive the damaging messages passively and “prepare” to die. Perhaps there is a window of opportunity to train cells to be more resilient.

Gap junctions are membrane channels that connect the cytoplasm of two adjacent cells. These junctions are abundantly expressed wherever perfect coordination is crucial. The best examples of these functions are in the heart and the central nervous system. Astrocytes are the major coordinators and the major gap junction bearers in the brain and spinal cord. Like myocytes in the heart, astrocytes express connexin (Cx)43, the building block for gap junctions. One amazing clinical phenomenon in cardiology is “ischemic precondition,” in which patients who experience a brief episode of mild ischemia later develop resistance and gain better survival potential against a “would-be” lethal blow in the near future. Cx43 has been established as the critical element in precondition.

In addition to empowering the cells to be resistant, Cx43 is also responsible for propagation of death signals. Understanding these seemingly conflicting roles of connexin is of the utmost importance to identifying an approach for minimizing the spread of injury while harnessing the injury into an initiating tool to maximize cells’ potential to develop resistance against secondary damage.

Research here has found that upon a brief exposure to a sublethal insult, Cx43 molecules are immediately recruited via endocytosis to the Golgi complex. This tremendous burst of Cx43 is followed by trafficking of the protein to a membrane where, as hemichannels, it releases adenosine triphosphate (ATP). ATP is subsequently degraded into adenosine, a well-established neuroprotective agent. Before the lethal challenge occurs, these Cx43 molecules are stored in lysosomes and ready to present themselves once again as

neuroprotectors. These results demonstrate that precondition not only removes Cx43 from the membrane, so as to stop cell-to-cell communication, and hence, injury propagation; it also turns Cx43 into retaliation weaponry to be ready to arm the cells with protective molecules when the true challenge arises. This phenomenon has been studied successfully and efficiently only in cultured cells, but may hold significant clinical implications upon future exploration.

- **Alexandra Joyner, Ph.D., Memorial Sloan-Kettering Cancer Center, “Genetic and MRI Studies of Spinal Cord Stem Cells,” January 1, 2006 – December 31, 2009 CART award.**

Spinal cord injury (SCI) is a serious health burden that now affects more than 200,000 Americans. Since in most SCI cases the spinal cord (SC) does not replace damaged cells or re-establish functional neural connections, recovery is minimal. The aim of this research project is to determine whether endogenous adult spinal cord neural stem cells (NSC) can be induced to expand, migrate to the injury site and differentiate into appropriate cell types following SCI. The premise of this work is that the most effective therapeutic approach for SCI would be to mobilize the resident NSC in the spinal cord to mediate recovery.

This study addresses two critical questions: where are NSC in the adult spinal cord, and what is their potential for repair of SCI? To identify and characterize SC NSC, the collaborating laboratories in this study are developing both genetic and live imaging (micro-MRI) tools to label and follow SC NSC in response to SCI. The plan then is to infuse molecules such as growth factors into the SC to test their ability to induce proliferation and migration of NSC to sites of SCI and/or promote differentiation of cells that repair the injury functionally.

The Turnbull laboratory at New York University Medical Center has made further progress in developing micro-MRI methods for imaging the mouse SC and characterizing SC lesions from *in vivo* images. This project has been aided by acquisition of a new Bruker Biospin Avance II console, which will yield a significantly higher image quality for the spinal cord studies proposed, as described in the research plan for this purpose. Notably, a novel gating method has been implemented on the new system and demonstrated to afford improvements in image quality in the cervical and thoracic spinal cord, without compromising image quality in regions of the image unaffected by motion. The Joyner laboratory has progressed in its short- and long-term cell-labeling experiments using Gli1-CreER and Nestin-CreER lines in combination with the *R26R-STOP-/acZ* reporter line. A potentially important new finding from preliminary fate mapping studies is that GFAP-expressing astrocytes in the spinal cord and brain respond to Shh signaling in the adult uninjured mouse. Although the predominant neural stem cell population in the adult forebrain has been shown to express GFAP, it is unknown whether neural stem cells in the adult spinal cord also express GFAP and whether these cells are dependent on Shh. Finally, Dr. Garcia is learning how to generate, maintain and differentiate adult spinal cord-derived neurospheres in order to characterize the sphere-

forming potential of marked cells in the spinal cord. Dr. Garcia also recently completed a Spinal Cord Injury Research Techniques short course at the University of California, Irvine.

The Turnbull laboratory will soon test its MRI methods on mice with SCI, applying the methods learned. Lesion volume will be detected and monitored over time with non-invasive MRI. Magnetically labeling and tracking the SC NSC following SCI will then be attempted. The Joyner laboratory will continue to characterize Gli1- and Nestin-marked cells in the normal SC and begin to study the changes following SCI. These investigators will also begin to test whether mutations in *Gli2* and *Gli3* abrogate repair.

In summary, this study employs a unique strategy of combining noninvasive MRI to visualize SCI and its repair over time, as well as a higher-resolution genetic approach for labeling and studying adult NSC, to build a foundation for developing similar therapies for human SCI. The studies will generate information on cells in human SC likely to be NSC and on visualization of NSC in human SC using MRI, and will suggest proteins to mobilize resident NSC for repair. Moreover, all the mouse MRI approaches developed in this project should have direct human correlates for translation into the clinical setting.

- **Gordon Barr, Ph.D., Research Foundation for Mental Hygiene, Inc., “Gene Expression After Acute and Chronic Injury and Rescue,” January 1, 2006 – December 31, 2009 CART award.**

This project calls for microarray and Q-PCR studies to yield detailed information about the time course of expression of genes associated with neuronal cell death or atrophy and a frustrated regenerative effort. Chronically injured neurons do not regenerate as readily as newly injured ones, probably because they express different or attenuated patterns of regeneration-associated genes. Chronically injured axons do regenerate into peripheral nerve grafts, but only if additional trophic factors are administered. Patterns of gene expression in chronically injured lateral vestibular nucleus neurons presented with a peripheral nerve graft and glial cell-line-derived neurotrophic factor (GDNF) will be identified to compare the effects of grafts into chronic and acute lesions. Control animals will receive GDNF, but will have no substratum for axonal regeneration. Results will suggest treatments for chronic injury, providing important information about the neural and genetic mechanisms of neuronal death, survival, axonal growth and regeneration, as well as insights into why various treatments for spinal cord injury may or may not work. These findings may then guide the development of novel treatments for human spinal cord injury.

The overall findings to date may be described as follows. Few changes occurred at four hours, but expression of large numbers of genes occurred from 24 hours through 42 days, with the most dramatic alterations beginning at three days following lesion. In general, early changes were more localized to the plasma membrane and involved cell signaling processes, including G-protein signal transduction genes. At three days of age, alterations in cytosolic processes began with alterations in genes related to microtubules

and biogenic amines. At seven and 14 days postoperatively, large increased expression of nuclear transcription factors such as JUN, RET and others was observed; substantial changes related to the axon, including microtubules, myosin and chromatin, as well as decreased glycolysis, energy metabolism and altered fatty acid synthesis were seen. At 42 days following lesion, although many changes found at seven and 14 days persisted, fewer of the cytosolic and energy metabolism shifts continued, and again, gene expression related to the plasma membrane and cellular communication was altered. These data describe detailed sequences of gene expression in cells as they were injured, began to die or recovered over a six-week period following axotomy.

- **Victor Arvanian, Ph.D., State University of New York at Stony Brook, “Neurotrophins and Function of the Injured Spinal Cord,” January 1, 2006 – December 31, 2009 CART award.**

Given the difficulty of guiding regenerating axons to the appropriate postsynaptic site, this project explores a strategy aimed at strengthening synaptic effects of the descending fibers that survive spinal cord injury to enhance function. This novel approach may reduce significantly the number of potential barriers to spinal cord repair that must be overcome to restore function and should be applicable to almost all patients with SCI. In order to study functions of survived connections in damaged spinal cord, this laboratory recently studied synaptic transmission at survived fibers following partial lesion of spinal cords in neonatal and adult rats.

Current studies investigate whether prolonged administration of neurotrophin NT3, combined with enhancing activity of glutamate N-methyl-D-aspartate (NMDA) receptors in motoneurons, is safe and will induce strengthening of synaptic connections in the damaged spinal cords of neonatal rats. It was found that administration of NT3 via fibroblasts, combined with transient enhancement of the activity of NMDA receptors via NR2D-expressing herpes simplex virus type-1 (HSV-1) amplicon vector (HSVnr2d; U.S. Patent 11/313, 262 pending), induced appearance of new functional connections with individual motoneurons in damaged spinal cords of neonatal rats, and facilitated recovery of function in rearing and swimming behavioral tests of rats that underwent spinal injury as neonates. Importantly, this combinatorial treatment is safe and does not result in adverse effects on motoneurons' properties.

To investigate whether transgene delivery of NT3 and NMDA-2d subunits will strengthen synaptic connections and improve functional recovery following hemisection spinal cord injury in adult rats, a new technique was developed to record intracellularly *in vivo* from individual L5 motoneurons below injury synaptic responses evoked by stimulation of the descending ventrolateral funiculus fibers above the injury level (lateral hemisection at T10, recording from L5 motoneurons, stimulation of T6 VLF). It was found that lateral hemisection of the spinal cord at T10 produces interruption of synaptic transmission across the injury level in adult rats. Importantly, combinatorial treatment with NT3 and HSV-NR2D induced appearance of polysynaptic responses across the injury region in some animals. Even though NT3+HSVnr2D-produced recovery of

synaptic connections in the damaged spinal cords was partial and occurred only in about 30 percent of animals tested, this is the first known demonstration of partial recovery of functional connectivity to individual motoneurons in the damaged spinal cord of adult mammals.

- **Holly Colognato, Ph.D., State University of New York at Stony Brook, “Remyelination and Spinal Cord Injury,” January 1, 2006 – December 31, 2009 CART award.**

In the majority of spinal cord injuries, a subset of nerves survive injury. However, these surviving nerves may not function properly or may undergo degeneration subsequent to the initial injury. One reason this deterioration might occur is the loss of myelin, the protective insulating coat that normally surrounds nerves (myelin is also damaged or destroyed during spinal cord injury). Recently, it was discovered that in addition to being required for nerve signal transmission, the myelin coat is necessary to protect nerves from degeneration and death. Therefore, without myelin, nerves that survive the initial injury die during the injury aftermath. Myelin is produced by specialized glial cells; however, at present, it is unknown how to stimulate the survival of these glial cells or how to reactivate myelin production following spinal cord injury. Several signaling mechanisms and molecules that control glial cell survival and myelin production during normal nervous system development have been discovered. Thus, it is important to address whether elements of the injury environment can stimulate glial cell survival and myelin production, and, if so, whether this stimulation leads to enhanced recovery from spinal cord injury.

Studies here suggest that signaling through an enzyme called Csk can modulate survival in cell culture models. Under development is a mouse model of Csk deficiency to test whether Csk is important for myelin-producing cells’ survival following spinal cord injury.

A molecule called laminin, found on nerve surfaces, has been linked to normal myelin formation (children born without the laminin gene develop severe muscular dystrophy, as well as abnormal myelin in the brain). Studies are underway to assess whether laminin molecules play a role in spinal cord remyelination following injury, by characterizing the expression of laminins and laminin receptors following injury.

Also undergoing testing are approaches to manipulating immune cells to stimulate expression of these promyelination factors, with the goal of stimulating remyelination and fostering spinal cord recovery. Mice with inhibited immune cell activation are characterized and studied to determine how the timing of immune modulation influences the survival of neural cells.

- **Blair Calancie, Ph.D., SUNY Upstate Medical University, “Repair of *Cauda Equina* Injury,” January 1, 2006 – December 31, 2009 CART award.**

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*. This injury may result in loss of muscle function in the legs and bladder (paralysis), loss of sensation, and sometimes, chronic burning pain. About one in five persons admitted to the hospital with spinal cord injury actually has *cauda equina* injury. At present, no treatment is available for such nerve damage, and the chances for natural recovery are poor. Development of an effective treatment is planned using a combination of molecules to enable nerve growth and reduce scar tissue, to be delivered through tiny particles (nanospheres) that dissolve after placement at the site of injury, slowly releasing their contents.

In an adult rat, damage to the *cauda equina* is noted in the control of tail movement. Therefore, this laboratory has “mapped” the location of spinal cord nerves that connect with major muscles controlling tail movements in the noninjured (that is, intact) adult rat. This mapping is performed by injecting dye into the muscle, to be then transported back to the spinal cord for viewing under special microscopes. These anatomy studies are combined with work using electrical stimulation of nerves to the tail muscles in order to compare anatomy and physiology studies. To date, findings from both investigations have been generally in good agreement. Next, a three-dimensional movement analysis of the rat tail during tasks in which the rat uses the tail for balance was developed. By placing small reflective markers along the tail, exact measurements of tail position, movement speed and angles while the rat is walking can be measured. This method will allow us comparison of the recovery of tail function with high accuracy, as studies progress in the injured animal and treatment approaches are introduced using nanospheres.

- **Dennis J. Stelzner, Ph.D., SUNY Upstate Medical University, “Local Release of Chondroitinase to Treat Spinal Cord Injury,” January 1, 2006 – December 31, 2009 CART award.**

Axonal regeneration is limited by several molecules expressed after spinal cord injury (SCI), including components of the glial scar, in particular, chondroitin sulfate proteoglycans (CSPGs). Neutralizing these inhibitory factors, for example, by removing the inhibitory side chains of CSPGs (GAGs) with the enzyme chondroitinase ABC (cABC), can enhance axonal growth, but this therapy has not been completely successful, either because the enzyme loses its effectiveness or is not localized to the scar, or because additional factors inhibit further regeneration. This project is designed to: 1) fabricate nanoparticles made of a polymer (PLGA) with which cABC is incorporated, and in a size range less than a micron in diameter so that they can be easily injected (nanospheres); 2) characterize the release properties of the nanospheres, and determine whether and for how long the released cABC remains enzymatically active by removing the GAGs and

enhancing axonal growth in a cell culture model; and 3) determine whether cABC injections into SCI will also remove GAGs acutely or after the glial scar has formed, and whether axonal regeneration and recovery of function will follow this treatment. It is hypothesized that other therapeutic agents incorporated into nanospheres will stimulate regeneration in future experiments, and that release of several factors in a combined approach ultimately will prove most effective.

Methods to produce the nanospheres have been altered so that their size range may be better controlled. Experiments are underway to determine how to limit the uptake of nanospheres by scavenger cells (macrophages) in culture and after injury. The effect of releasing various amounts of cABC in a culture system is being determined, noting that loading too high a concentration of cABC into nanospheres results in toxicity not observed at the initial level.

In culture and after SCI, enzymatically active cABC has been found to be localized to a 2.5-mm region surrounding the injection site, and released for one month in culture and for at least two weeks in the injured spinal cord. The cABC removes GAGs from the CSPGs and induces axonal growth in a SCI lesion by seven days after injury, growth that increases significantly by one month post-SCI.

Another project, not proposed in the original application, needed to be conducted to characterize the response of short- and long-distance propriospinal tract (PST) axons to moderate spinal contusion injury, in anticipation of using propriospinal axons to test the effectiveness of cABC nanospheres in enhancing neural plasticity and axonal regeneration after SCI (Experiment 3). Among the findings was that short PST axons are severely damaged, but many of these PST neurons survive this damage for several weeks and are positioned so that cABC nanosphere injections are likely to foster the regeneration of the PST axons.

- **Xiang Yang Chen, Ph.D., Wadsworth Center, NYS Department of Health, “Using Reflex Conditioning to Restore Spinal Cord Function,” January 1, 2006 – December 31, 2009 CART award.**

Spinal cord injuries lead to abnormal spinal reflexes, and these abnormal reflexes contribute to motor disabilities. Studies for many years here have shown that operant conditioning can change spinal cord reflexes in monkeys, rats, mice and humans, including humans with partial spinal cord injuries. Recent work in rats shows that soleus H-reflex conditioning changes soleus behavior during locomotion, and that this reflex conditioning can improve locomotion in spinal cord-injured rats. This finding indicates that spinal reflex conditioning could be an important new method for inducing and guiding spinal cord plasticity to help restore function after spinal cord injury. The central goal of this research is to develop further operant conditioning of spinal reflex as a new therapeutic approach and establish its clinical value for humans with spinal cord injuries.

Specifically, this project will: 1) determine the capabilities, characteristics and long-term efficacy of this new treatment method, by testing in rats with well-defined spinal cord lesions, the effects on locomotion of carefully selected conditioning protocols ; 2) define anatomical and physiological plasticity induced by reflex conditioning; and 3) establish the clinical value of this new therapeutic approach by determining in patients with partial spinal cord injuries whether appropriate reflex conditioning can improve locomotion and whether this improvement persists. The results of studies to date have been published in four highly regarded scientific journals. Additional manuscripts are nearing completion. Next steps include making appropriate modifications to the human H-reflex conditioning protocol for application to patients with partial spinal cord injuries and evaluating the effects of spinal cord reflex conditioning on motor function in subjects with spinal cord injuries.

Successful completion of this project should introduce a new therapeutic method for restoring function after spinal cord injury. This method may prove applicable to functional deficits other than defective locomotion (such as spasticity), and could be readily automated so as to minimize the need for continuing involvement of therapists and other health care providers. Furthermore, once techniques for achieving significant spinal cord regeneration become available, reflex conditioning protocols will be valuable, perhaps even essential, for reeducating the restored spinal cord to function effectively.

- **Maria Knikou, Ph.D., City University of New York, “Sensorimotor Control of Spinal Locomotor Centers in Human SCI,” January 1, 2006 – December 31, 2007 IDEA award.**

Stepping on a treadmill while body weight is supported by a harness with “as needed” manual assistance from trainers is one of the main tools for walking re-training of individuals with spinal cord injury (SCI). This intervention maximizes sensory feedback from leg receptors that play a significant role in reflex regulation of walking, as postulated by experimental studies in despinalized or decerebrated animals. However, the effects of sensory feedback on spinal reflex circuits and reflex regulation during this intervention are largely unknown. This project uses spinal reflexes as neurological probes to establish the expression of spinal reflex circuits during assisted stepping in patients with SCI. The main objectives of this project are to characterize spinal reflex excitability (H-reflex and flexion withdrawal reflex), and spinal inhibitory control systems during assisted stepping as a function of sensory input from the hip region and foot sole.

All algorithms for data acquisition and analysis have been developed, while three experimental sessions have been completed in eight subjects with established SCI who have consented to participate in all experimental sessions associated with this research project. In this context, the following findings have been made: 1) the recruitment curves of the M-wave and H-reflex, with the subjects supine, seated and standing on a treadmill while some body weight is removed to avoid knee buckling during standing; 2) the modulation pattern of the soleus H-reflex during assisted stepping on a treadmill; and

3) the amount of reciprocal Ia inhibition exerted from ankle flexors to ankle extensor motoneurons, with the subjects supine, seated and standing, and during assisted stepping on a treadmill. During these tests, bilateral activity of eight leg muscles; position of hip, knee and ankle joints; and stance/swing phase duration have been recorded simultaneously.

The findings of this project are anticipated to have great impact on rehabilitation of walking in people with SCI. These discoveries will aid understanding of spinal reflex circuit functioning after a lesion of the central nervous system during a functional motor task, such as stepping on a treadmill. Thus, the work will assist in maximizing this intervention based on the actual behavior of the spinal reflex circuits, not just on clinical observations. To conclude, new avenues of research should be opened in the field of translational neuroscience, with the sole aim of promoting sensorimotor recovery in these patients.

- **Dimitar Nikolov, Ph.D., Memorial Sloan-Kettering Cancer Center, “Structural Study of Axon-Inhibitory Factors in the Spinal Cord,” January 1, 2006 – December 31, 2007 IDEA award.**

Following spinal cord injury, a number of cellular events restrict the extension and re-growth of spinal cord neurons. As a result, any impairment of function is lasting and often permanent. Many lines of evidence suggest that a number of secreted and cell-surface inhibitory molecules act on spinal cord neurons and are, at least partially, responsible for this lack of neuronal recovery. These molecules include the semaphorins, which act through their plexin and neuropilin receptors, as well as several myelin-specific proteins, including Nogo-A, MAG and OMgp. It is noteworthy that all myelin-specific inhibitory factors appear to act through a central receptor, the Nogo receptor (NgR), thus highlighting the importance of this molecule in efforts to stimulate recovery after central nervous system (CNS) damage.

During the past several years, this laboratory has made important progress toward understanding the molecular events underlying the signaling events that regulate neuronal behavior in the spinal cord. Specifically, the crystal structures of Semaphorin-3A and the Nogo receptor have been determined, and a detailed analysis of the interaction of Semaphorin-3A and Nogo with their receptors has been performed. Efforts are now underway to utilize X-ray crystallography to determine the structure of semaphorins and Nogo bound to their neuronal receptors and coreceptors, as well as to implement structure-based and structure-independent high-throughput screens for small molecules that could block the action of these inhibitory molecules and promote neuronal regeneration in the spinal cord.

- **Takeshi Sakurai, Ph.D., Mount Sinai School of Medicine, “Enhancement of Remyelination by Modulating RPTP $\alpha$  Activity,” January 1, 2006 – December 31, 2007 IDEA award.**

The laboratory’s overall goal is to optimize post-spinal cord injury myelination and formation of nodes – structures crucial for supporting efficient nerve conduction – to achieve optimal functional recovery from such injury. The objective of this project is to regulate myelination and node formation by modulating the activity of RPTP $\alpha$ , an enzyme that plays crucial roles in these processes. To this end, three specific aims are under investigation: 1) to locate RPTP $\alpha$  activity in cells during myelination; 2) to study the effects of RPTP $\alpha$  activity modulation in myelinating cultures; and 3) to characterize the effects of RPTP $\alpha$  activity modulation in animals.

Myelinating cultures of the peripheral nervous system (PNS) were used to purify oligodendrocyte cultures. It was found that: 1) RPTP $\alpha$  is expressed in both neurons and myelinating glial cells, as well as all processes of these cells, suggesting that localization of RPTP $\alpha$  substrates in the cells could determine RPTP $\alpha$  activity effects during myelination; and 2) overexpression of RPTP $\alpha$  inhibits myelination by Schwann cells *in vitro*, and perturbs oligodendrocyte differentiation *in vitro*. Based on these results, it is posited that overexpression of RPTP $\alpha$  in these glial cells may slow down remyelination processes after spinal cord injury.

If the above hypothesis is true, conversely, perturbing RPTP $\alpha$  activity by inhibitors may enhance myelination. Moreover, RPTP $\alpha$  knockout mice will be analyzed to determine whether: 1) myelination is enhanced in animals; and 2) remyelination after demyelination is enhanced in the same animals. Finally, if specific inhibitors of RPTP $\alpha$  are found that would improve myelination *in vitro*, these inhibitors will be used in the animals after demyelination to ascertain whether remyelination is improved. Through these analyses, it is hoped that RPTP $\alpha$  may be established as a therapeutic target for promoting remyelination processes after spinal cord injury.

- **Wen-Biao Gan, Ph.D., New York University School of Medicine, “The Role of Microglia in Axon Regeneration Following Spinal Cord Injury,” January 1, 2006 – December 31, 2007 IDEA award.**

Following spinal cord injury (SCI) and traumatic brain injury (TBI), a glial scar forms progressively over time and is detrimental to neuronal regeneration. Microglia are the first cells to enter the site of injury, but their role in scar formation and neuronal regeneration remains unclear. In this project, the dynamic behavior of microglia was examined over time following SCI and TBI in living transgenic mice expressing green fluorescent protein in microglia and yellow fluorescent protein in neurons. Using a two-photon laser ablation method, focal injury in the superficial dorsal funiculus of the spinal cord and the superficial cortical layer 1 was reliably produced. Laser ablation can be targeted to individual axons while leaving nearby axons ~30  $\mu$ m away intact. This study

indicated that damaged axons degenerated and retracted ~200  $\mu\text{m}$  within the first two hours after injury and failed to regenerate within days. Using this laser-induced injury model, it was found that even though fewer microglia existed in the spinal cord dorsal column than in the superficial somatosensory cortex, microglial responses following SCI and TBI were similar. Consistent with previous work on the cerebral cortex, microglial processes moved rapidly toward and wrapped around the site of injury in the spinal cord within one hour, suggesting that the initial responses of microglia may be involved in confining damage and preventing the spread of deleterious substances. Microglial somata were relatively stable within the first three hours after both TBI and SCI.

However, accumulation of microglial somata was observed in the vicinity of the lesion after 12 hours. The aggregated microglia persisted during the next ten days and constituted an important part of the glial scar. Associated with microglial response to the injury was an elevated calcium level in astrocytes surrounding the lesion site, suggesting that astrocytes may serve as a signal for microglial migration for hours to days. Current investigation focuses on a means to prevent the accumulation of microglia at the lesion site. New methods to remove microglia from existing scar tissues are also in development to reduce the glial scar and enhance axon regeneration. These studies will offer the first glimpse at microglial response, scar formation and axonal regeneration following spinal cord injury and will test treatments aimed at enhancing axonal regeneration.

- **Joseph A. Helpert, Ph.D., and Ray F. Lee, Ph.D., New York University School of Medicine, “*In vivo* MR Microscopy of the Human Spinal Cord at 7 Tesla,” January 1, 2006 – December 31, 2007 IDEA award.**

The ability of magnetic resonance imaging (MRI) at high magnetic field strengths (i.e., 7 Tesla) to detect small changes in tissue structure and function will yield unique information in patients with spinal cord injury (SCI). It is predicted that imaging will enable more specific classification of SCI by detecting lesions previously unseen by conventional MRI. This project aims to build and test radio frequency (RF) coils for spinal cord MRI at a high magnetic field strength of 7 Tesla. The most challenging technical aspect of MRI at 7 Tesla lies in development of strategies for RF coil construction and management of RF power deposition, which must remain within acceptable limits for humans.

The first coil design included four loops and four strips and was mainly driven by the linear anatomical presentation of the spinal cord. This coil was designed to transmit RF power with four strips and receive the RF signal with the four strips and four loops. Testing and modification continues with this coil, and design of another coil for a different approach is underway. This new coil consists of a volume RX/TX coil based on a 30cm ID x 20cm long shielded resonator. Simulations show that this coil design will achieve an approximately 0.3uT B1 field with 1W input, ignoring non-subject losses from 35 to 60 percent of the values achieved with a similar-sized volume coil located for optimal transmit efficiency in the human brain. Despite its smaller size, the neck shows

marked B1 nonuniformities, although the field provided by this arrangement would have suitable homogeneity over the upper cervical spine. Bench-testing the coil's performance remains an essential step before attempting imaging in humans. The impact of this work is significant, since it should lead to the first-ever 7 Tesla images of human spinal cord.

- **Kyonsoo Hong, Ph.D., New York University School of Medicine, "Sema3A-Induced Ca<sup>2+</sup> Signaling in Xenopus Spinal Neurons," January 1, 2006 – December 31, 2007 IDEA award.**

Cell surface membrane potentials gate ion channel conductance that control various neuronal functions in response to external signals. Diffusible guidance molecules guide growth cones – the tips of growing neurites – by modulating intracellular second-messenger signaling pathways via a poorly understood mechanism. It was found that diffusible guidance molecules cause different patterns of membrane potential shifts, and that these result in either growth-cone repulsion or attraction. The repellents Sema3A and Slit2 cause membrane potential shifts towards hyperpolarization, while the attractants netrin-1 and BDNF cause potential shifts towards depolarization. These membrane potential shifts occur independent of Ca<sup>2+</sup> entry and require activation of either Cl<sup>-</sup> or Na<sup>+</sup> channels during Sema3A signaling. Clamping the growth-cone membrane potential at the resting potential prevented Sema3A-induced growth-cone turning. Clamping to depolarization was sufficient to convert Sema3A-induced repulsion to attraction, and clamping to hyperpolarization had no effect on repulsion. Repulsive Sema3A increased cGMP levels via soluble guanylyl cyclase, leading to fast onset and long-lasting membrane hyperpolarization. A pharmacological increase in cGMP levels caused protein-kinase-G (PKG)-mediated depolarization, which switched Sema3A-induced repulsion to attraction. These findings indicate that diffusible guidance molecules likely function by causing membrane potential shifts, and that cyclic nucleotide signaling mediates these shifts, revealing a novel molecular switching mechanism involved in growth-cone guidance.

- **James Salzer, Ph.D., New York University School of Medicine, "Role of Neuregulin 1 in Spinal Cord Remyelination," January 1, 2006 – December 31, 2007 IDEA award.**

Functional recovery of the injured spinal cord requires that nerve fibers regrow across the injury site, find their appropriate targets within the spinal cord and become covered by myelin, an insulating sheath that surrounds nerves. The myelin sheath is essential for impulse conduction and protects and maintains the integrity of nerve fibers. Indeed, loss of myelin, or demyelination, results in progressive degeneration of axons and is believed to be a significant contributor to the disability of spinal cord injury. Enhanced remyelination is, therefore, an important goal in treating spinal cord injury. Considerable evidence indicates that nerve fibers trigger the formation of this myelin sheath, but the signals involved have been elusive. Recently discovered here was that a growth factor on the axon surface, neuregulin (NRG), seems to enhance myelin formation in the brain.

This study aims to determine whether NRG also controls myelin formation in the spinal cord and might, therefore, be useful to promote new myelin formation (remyelination) after injury in the adult spinal cord. This determination, in turn, will serve two important goals: 1) neuroprotection, and 2) overcoming blocking of impulse propagation.

Several approaches are underway to study the role of NRG1 in spinal cord myelination. One strategy has been directed to comparing the amount of myelin that forms during normal development in the spinal cord of mice with only one copy of a key form of NRG1 versus normal mice, which have two copies. These data have shown that in contrast to the brain, the spinal cord is myelinated normally. The findings demonstrate unexpected heterogeneity in the signals that control myelination in various regions of the central nervous system (CNS) – an emerging theme in recent myelin research. To assess the role of NRG1 in spinal cord myelination and remyelination more definitively, the plan is to eliminate all copies of the NRG1 gene in neurons expressed in the spinal cord. This strategy calls for a set of crosses among different mouse strains. The work confirms an important role for NRG1 in peripheral nervous system development and likely myelination, and suggests that this role may be less critical in the CNS. The present goal is first to clarify NRG1 requirements for normal development, then extend the analyses to models in which the spinal cord, and possibly the brain, are demyelinated, and then ask whether NRG1 is required for remyelination.

- **Ben G. Szaro, Ph.D., SUNY University at Albany, “Gene Expression Profiling in Successful Spinal Reinnervation,” January 1, 2006 – December 31, 2007 IDEA award.**

The objective of this project is to identify genes on gene array chips that change their expression significantly in individual neurons that successfully regenerate an axon whenever the spinal cord is severed in tadpoles. These neurons are the same as those that in humans send signals for movement from the brain to the spinal cord. A state-of-the-art microsurgical laser is used to dissect these neurons from sections of brainstem harvested at various times after injury. The first step has been to follow, by *in-situ* hybridization, changes in individual genes' expressions already known to change during optic axon regeneration. These genes will serve as a reference point for spinal cord studies. The second step is to study the expression of tens of thousands of genes at once with gene arrays to look for those whose expressions correlate with successful regeneration. In the third step, key candidate genes will be modified in transgenic frogs and tadpoles to determine those that play essential roles in spinal cord axon outgrowth. Last year, this laboratory published findings that large reticular magnocellular neurons are among those that regenerate an axon successfully if the spinal cord is cut in tadpoles. In the past six months, characterization of changes in expression of four separate genes that responded during optic nerve regeneration has been completed – two of these genes (NF-M and GAP43) responded similarly in spinal cord and optic nerve. Another gene (musashi), because it is only expressed in proliferating neuronal stem cells, demonstrated that spinal cord axon regeneration in frog occurs without neurogenesis. Optimizing the recovery of RNAs from neurons sampled by laser capture microdissection has proved necessary,

because methods on mammalian brain proved inadequate for frog tissue. Finally, plasmids are in preparation, and antisense methods for manipulating gene expression in embryos and tadpoles are being tested ahead of functional studies. The next steps are: 1) to follow the expression of reference genes in samples prepared from regenerating spinal cord by laser capture microdissection; and 2) to proceed to analyzing samples on gene arrays. This work will identify potential targets for gene therapy approaches to treating spinal cord injury in humans.

- **Roman Giger, Ph.D., and S.-S. Sheu, Ph.D., University of Rochester, “Calcium Trap for the Myelin-Associated Glycoprotein Receptor,” January 1, 2006 – December 31, 2007 IDEA award.**

The primary focus of this study is to gain insights into the molecular mechanisms by which the myelin inhibitor MAG signals growth inhibition to injured neurons. To address this question experimentally, a combination of mouse genetics, molecular biology and calcium ( $\text{Ca}^{2+}$ ) imaging in primary neurons is used. Understanding the mechanisms of MAG-elicited growth inhibition will allow development of strategies aimed at promoting neuronal growth and restoring neuronal contacts lost as a consequence of injury.

Although spinal cord injury (SCI) causes complex damage, a large portion of the basic circuitry to control movement remains intact, because the spinal cord is arranged in layers of circuitry. Many of the connections and neuronal cell bodies forming this circuitry are located above or below the site of injury, and thus, are spared. Therefore, an important question in spinal cord injury research is how to promote regenerative axonal growth of injured neurons in order to reestablish lost neuronal connectivity. It is a well-known fact that following injury to the adult mammalian central nervous system (CNS), axonal growth is extremely limited. As a result, CNS trauma generally results in severe and persistent functional deficits. The inability of CNS neurons to initiate long-distance regenerative axonal growth spontaneously is primarily a reflection of the growth-inhibitory nature of adult mammalian CNS tissue. Inhibition is mediated by glial scar tissue formed by reactive astrocytes and other cell types. In addition, CNS myelin is a strong inhibitor of axonal growth, and multiple lines of evidence suggest that antagonism of CNS myelin-associated inhibitors leads to improved anatomical and functional recovery following SCI *in vivo*. The “myelin hypothesis” is based on these findings and predicts that partial or complete neutralization of myelin inhibitors (or their mechanisms) is a necessary step to achieve significant axonal growth following SCI.

Similarly to NgR1, the Nogo receptor family member NgR2 is linked to the neuronal plasma membrane by a glycosylphosphatidylinositol (GPI) anchor, and thus, it is not clear how, upon ligand binding to NgR1 or NgR2, the growth inhibitory signal is propagated across the neuronal plasma membrane. Because NgR1 and NgR2 are structurally very similar proteins, it was necessary to discern whether previously identified NgR1 receptor components also participate in NgR2 signaling. Binding studies in COS-7 cells revealed that NgR2 did not support binding of soluble ectodomain of

Lingo-1, TROY or *p75*. *V. cholerae* neuraminidase (VCN) and mouse genetics were also employed to probe the molecular composition of the MAG receptor complex in postnatal retinal ganglion cells (RGCs). It was found that VCN treatment was not sufficient to release MAG inhibition of RGCs; however, such treatment did significantly attenuate MAG inhibition of cerebellar granule neurons. Furthermore, loss of *p75* was not sufficient to release MAG inhibition of RGCs; however, *p75* null dorsal root ganglion (DRG) neurons showed enhanced growth on MAG, compared to wild-type controls. Interestingly, TROY was not a functional substitute for *p75* in RGCs. Finally, *NgR1* mutant RGCs were strongly inhibited by MAG. In the presence of VCN, however, *NgR1* mutant RGCs exhibited significantly enhanced neurite growth. Collectively, these studies revealed distinct and cell-type specific mechanisms for MAG-elicited growth inhibition.

- **Mark Noble, Ph.D., University of Rochester, “Remyelination of SCI: Overcoming the Inhibitors,” January 1, 2006 – December 31, 2007 IDEA award.**

Inhibition of regeneration in the injured spinal cord involves not just inhibition of axonal growth, but also a failure to restore patterns of myelination properly. The overall goal of this research is to understand how to overcome the limitations to myelination associated with spinal cord injury, and thus, develop rational approaches to enhancing this important aspect of repair.

Here, major progress has been made toward understanding the mechanistic basis for an approach that, from published reports, appears to offer the prospect of enhancing remyelination in SCI. This progress is based on the integration of research from other laboratories on a protein called LINGO-1 and on work in this laboratory on a newly discovered regulatory pathway that integrates multiple signals regulating oligodendrocyte generation from their ancestral progenitor cells (i.e., oligodendrocyte progenitor cells, or OPCs). Work by others has shown that LINGO-1 (which stands for LRR and Ig domain-containing, Nogo receptor-interacting protein) is present on axons and on OPCs, and inhibits myelination. Attenuation of LINGO-1 function with dominant-negative LINGO-1, LINGO-1 RNA-mediated interference (RNAi) or soluble human LINGO-1 (LINGO-1-Fc) leads to differentiation and increased myelination competence. Conversely, axonal overexpression of LINGO-1 *in vivo* greatly inhibits myelination. Furthermore, others have shown that the effects of Lingo-1 appear to be oligodendrocyte-specific, as Lingo-1 does not influence Schwann cell myelination.

The linkage between the work by others on LINGO-1 and present analysis of control of oligodendrocyte generation occurs through an enzyme called Fyn kinase, which has long been known to play a critical role in oligodendrocyte generation and maturation. Antagonizing LINGO-1 (which promotes myelination) causes an increase in Fyn phosphorylation and, conversely, Fyn<sup>-/-</sup> mice are defective in oligodendrocyte generation.

Research here has shown that Fyn activation triggers oligodendrocyte generation by causing the ubiquitinylation-mediated downregulation of cell surface receptors critical for maintaining the division of oligodendrocyte progenitor cells. More specifically, activated Fyn phosphorylates c-Cbl, an E3 ubiquitin ligase-activated c-Cbl ubiquitylates platelet-derived growth factor (PDGF) receptor- $\alpha$  (PDGFR $\alpha$ ), the receptor for the major mitogen for OPCs, leading to downregulation of this receptor, cessation of cell division and initiation of differentiation.

Combined, these discoveries now enable dissection of the molecular mechanism by which antagonizing LINGO-1 promotes myelination, thus potentially yielding multiple rational means of rendering such enhancement more successful, and also, potentially revealing situations in which application of this therapy may actually cause more harm.

- **Samie Jaffrey, M.D., Ph.D., Weill Medical College of Cornell University, “Novel mRNA Regulatory Pathways Underlying Axon Growth in SCI,” January 1, 2006 – December 31, 2007 IDEA award.**

Injury to the spinal cord affects the axons that descend from the brain. The proximal portion of the injured axons attempts to regenerate and form connections with motor neurons in the spinal cord, but is inhibited by components in myelin. In general, adult axons lack the features normally seen in neurons of the developing brain that allow the axon to elongate and find its targets, such as growth cones, the structures at the tip of an elongating axon. However, after injury, axons form growth cone-like structures and may recapitulate other features of developing axons. One element thought to be particularly important for axonal elongation and pathfinding is the ability of the axon to translate mRNAs into proteins. This capability is lost in adult axons, but may reappear following injury. It is possible that myelin prevents axonal growth by interfering with axonal mRNA translation. Also, if injured axons can translate mRNA, then it is possible that this feature could be exploited in developing novel types of gene therapy, such as using RNA viruses to manipulate protein composition in injured axons. The goal of this research is to determine whether certain known mRNAs are present in regenerating mature axons; whether they can be translated there; whether myelin or its components regulate mRNA translation; whether myelin or its components require mRNA translation to mediate its effects; and whether a new class of molecules that regulate mRNA translation, i.e., microRNAs, are present in axons and regulate the translation of proteins that play critical roles in axonal elongation.

Several important discoveries have resulted from this project, including the findings that regenerating axons do indeed contain mRNAs, mRNAs are translated within axons, and axons contain a unique population of microRNAs. Next, the laboratory will identify specific mRNAs that might play a role in myelin signaling. Already, these findings indicate that mRNA translation is an important component of axonal regeneration.

- **Neeta S. Roy, Ph.D., Weill Medical College of Cornell University, “Development of Rodent-Human Chimeras for Study of Spinal Cord Injury,” January 1, 2006 – December 31, 2007 IDEA award.**

Bipotential progenitors capable of giving rise to both oligodendrocytes and motor neurons are uniquely specific to the developing ventral spinal cord (SC). Such progenitors would, therefore, be extremely useful for repair of acute spinal cord injury (SCI), in which both oligodendrocyte and motor neuron loss plays a major role in neurological deficits observed in patients.

These studies propose to determine the potential therapeutic utility of SCI repair by appropriately induced hES cell-derived bipotential progenitors selected on the basis of Neurogenin 2 (Ngn2) expression. Cells selected on the basis of this specific promoter will be transplanted in both the developing neural tube and injured adult rat SC, and assessed for: (a) engraftment competence; (b) differentiation potential; (c) structural integration; and (d) impact on functional improvement in the injured rats.

Here, it has been found that hES cell culture-derived progenitors survive in the spinal cord of adult rats subjected to SCI for as long as three months posttransplant. Behavior analysis determined that animals transplanted with hES cell-derived progenitors show marginally improved BBB scores, as compared to untransplanted injured control animals or animals transplanted with fetal SC-derived progenitors. Histological analysis of SC from sacrificed animals showed that fewer than 10 percent of the cells differentiate as motor neurons. Most of the transplanted population remains as bIII-tubulin-expressing or as nestin-expressing progenitors, while no cell expresses markers of hES cells. No evidence of quantifiable differentiation into oligodendrocytes has been seen at three months posttransplantation, although a few stray xenograft-derived MBP-expressing oligodendrocytes can be observed at the transplant site. In addition, no xenograft-derived axonal outgrowth from the injured SC to the peripheral system was observed. This finding indicates that longer time periods posttransplantation may be needed for appropriate and sufficiently different integration, and thus, improved functional recovery. Experiments are underway to address this issue.

Cells were successfully delivered into the neural tube of E7 rat embryos. However, unexpectedly, survival of the transplanted embryos was compromised in every attempt. At present, work is in progress to transplant cells at later embryonic time points to maximize survival.

## **VI. Publications Resulting from SCIRB-Funded Research**

During 2007, 20 papers and one textbook chapter, as well as numerous abstracts stemming from 12 of 52 SCIRB-funded projects active in 2007 were published or accepted for publication (Appendix III). Notably, 22 of these project contracts began in late 2007. Three patent applications also were filed (Appendix IV).

## **VII. Program Operations**

The Executive Secretary to the Board is Ms. Bonnie Brautigam.

The position of Health Program Administrator 2 was vacated in October 2007 and filled in November 2007. A new Health Program Administrator 1 position was created and filled in November 2007. The Program was integrated into the Wadsworth Center's Division of Laboratory Operations, where it now benefits from an existing administrative infrastructure. The positions of Associate Accountant, Laboratory Center Administrator 1 and Administrative Aide remained unchanged. The Program anticipates increased stabilization, enhanced communication with the Board and contractors, and reporting of landmark Board-funded research scientific advances in the coming year.

## **VIII. Fiscal Status of the Spinal Cord Injury Research Trust Fund**

Through December 31, 2007, cash deposits to the Trust Fund totaled \$59.5 million. Interest on unexpended funds rose to more than \$5.2 million, for a total of \$64.7 million in available cash since the inception of the Fund.

Cash disbursements from the Fund include: voucher payments on research contracts (\$31.7 million); payments on peer-review/miscellaneous contracts (nearly \$1.7 million); and administrative costs (\$2.1 million) over the life of the Fund.

Research contracts totaling up to \$7.5 million are expected to be awarded in 2008 with start dates of October 1, 2008, based on a Request for Applications (RFA) offering CART, IDEA, Mentored Scientist and Postdoctoral Fellowship awards.

It is expected that a deposit of \$8.5 million will be made prior to the end of the current State Fiscal Year, March 31, 2008. The State Finance Law provides for an annual deposit to the Fund not to exceed this amount.

**Appendix I**  
**Chapter 338, Laws of 1998, as Amended by Chapter 612, Laws of 1999**

**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.

**§ 3.** Article 2, section 17 of the public officers law is amended by adding a new paragraph (m) to read as follows:

(m) For the purposes of this section, the term “employee” shall include the members of the spinal cord injury research board within the department of health.

**§ 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.

§ 5. Article VI of the state finance law is amended by adding a new section 99-f to read as follows:

**§ 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.

§ 6. This act shall take effect January 1, 1999

**Appendix II**  
**NEW YORK STATE**  
**SPINAL CORD INJURY RESEARCH BOARD**  
**Bylaws**

**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

#### 2007 Publications Resulting from Spinal Cord Injury Research Board-Funded Projects

**C020922 Albany Medical College**

Project Title: Engineering Embryonic Spinal Cord Stem Cells for Spinal Cord Injury

Lowry, NA, and Temple, S (2007) Making Human Neurons From Stem Cells After Spinal Cord Injury. *PLoS Med.* **4(2)**, e48.

**C020932 Wadsworth Center, New York State Department of Health**

Project Title: Using Reflex Conditioning to Restore Spinal Cord Function

Wolpaw, JR, and Chen, XY (2007, in press) Spinal Cord: Operant Conditioning of Reflexes. Chapter In: Squire, L, T Albright, F Bloom, F Gage, and N Spitzer, Eds. *New Encyclopedia of Neuroscience*.

**C020939 New York University School of Medicine**

Project Title: Role of Neuregulin 1 in Spinal Cord Remyelination

Taveggia, C, Thaker, P, Petrylak, A, Caporaso, GL, Toews, A, Falls, DL, Einheber, S, and Salzer, JL (2007, in press) Type III Neuregulin-1 Promotes Oligodendrocyte Myelination. *Glia*.

**C020940 Research Foundation of SUNY/University at Albany**

Project Title: Gene Expression Profiling in Successful Spinal Reinnervation

Ananthakrishnan, L, Gervasi, C, and Szaro, B (2007, in press) Dynamic Regulation of Middle Neurofilament (NF-M) RNA Pools During Optic Axon Regeneration. *Neuroscience*.

**C020941 University of Rochester Medical Center**

Project Title: Calcium Trap for the Myelin-Associated Glycoprotein Receptor

Venkatesh, K, Chivatakarn, O, Sheu, SS, and Giger, RJ (2007) Molecular Dissection of the Myelin-Associated Glycoprotein Receptor Complex Reveals Cell Type-Specific Mechanisms for Neurite Outgrowth Inhibition. *J. Cell Biology* **177(3)**, 393-399.

Duan, Y, Gross, RA, and Sheu, SS (2007, in press) Ca<sup>2+</sup> Dependent Generation of Mitochondrial Reactive Oxygen Species Serves as a Signal for Poly (ADP-ribose) Polymerase-1 Activation During Glutamate Excitotoxicity. *J. Physiology*.

Chivatakarn, O, Kaneko, S, He, Z, Tessier-Lavigne, M, and Giger, RJ (2007) The Nogo-66 Receptor NgR1 Is Required Only for the Acute Growth Cone-Collapsing but not the Chronic Growth-Inhibitory Actions of Myelin Inhibitors. *J. Neuroscience* **27(27)**, 7117-7124.

**C018612 University of Rochester**

Project Title: Purinergic Signaling in Spinal Cord Injury

Takano, T, Tian, GF, Peng, W, Lou, N, Lovatt, D, Hansen, A, Kasischke, K, and Nedergaard, M (2007) Cortical Spreading Depression Causes and Coincides With Tissue Hypoxia. *Nature Neuroscience* **10(6)**, 754-762.

**C018614 City University of New York**

Project Title: Overcoming Myelin Inhibitors to Promote Regeneration *in vivo*

Spencer, T, Mellado, W, Chatila, TA and Filbin, MT (2007, in press) BDNF Activates CaMKIV and PKA in Parallel to Block MAG-Mediated Inhibition of Neurite Outgrowth.

Hannila, SS, and Filbin, MT (2007) The Role of Cyclic AMP Signaling in Promoting Axonal Regeneration After Spinal Cord Injury. *Exp. Neurol.* PMID: 17720160.

Cao, Z, Qiu, J, Domeniconi, M, Hou, J, Bryson, JB, Mellado, W, and Filbin, MT (2007) The Inhibition Site on MAG Is Within Ig-Domain 5 and Is Distinct From the Sialic Acid Binding Site. *J. Neuroscience* **27(34)**, 9146-9154.

Chaudhry, N, and Filbin, M (2007) Myelin-Associated Inhibitory Signaling and Strategies to Overcome Inhibition. Invited review. *J. Cereb. Blood Flow Metab.* **27(6)**, 1096-1107.

Hannila, SS, Siddiq, MM, and Filbin, MT (2007) Therapeutic Approaches to Promoting Axonal Regeneration in the Adult Mammalian Spinal Cord. *Int'l. Rev. Neurobiology* **77**, 57-105.

**C018615 Albert Einstein College of Medicine**

Project Title: Regulating Axon Guidance in the Vertebrate Spinal Cord

Imondi, R, Jevince, AR, Helms, AW, Johnson, JE, and Kaprielian, Z (2007, in press) Mis-Expression of L1 on Pre-Crossing Spinal Commissural Axons Disrupts Pathfinding at the Ventral Midline. *Mol. Cell Neurosci.*

**C018616 Albany Medical College**

Project Title: Implanted Neuroprosthesis for Exercise, Standing, and Transfers

Forrest, G, Smith, T, Triolo, R, Gagnon, J, DiRisio, D, Miller, M, Murray, L, Davis, J, and Iqbal, A (2007) Energy Cost of the Case Western Reserve Standing Neuroprosthesis. *Arch. Phys. Med. Rehab.* **88**, 1074-1076.

**C019772 Burke/Cornell Medical Research Institute**

Project Title: Center of Research Excellence – A Novel Multimodality Approach to Treating Spinal Cord Injury

Iseda, T, Kane-Goldsmith, N, Mathew, M, Ahmed, S, Chang, ., Young, W and Grumet, M (2007, in press) Single, High-Dose Intraspinal Injection of Chondroitinase Reduces GAGs in Injured Spinal Cord and Promotes Corticospinal Axonal Regrowth After Hemisection but not Contusion. *J. Neurotrauma*.

Kozikowski, *et al.* (2007, in press) Epigenetic Modulators and Their Role in Neuroprotection. *J. Med. Chem.*

Langely, B, *et al.* (2007, in press) Pulse Inhibition of HDACs Induces Complete Resistance to Oxidative Death in Cortical Neurons Without Toxicity and Reveals a Role for Cytoplasmic p21 waf1/cip1 in Cell Cycle Independent Neuroprotection. *J. Neuroscience*.

Ratan, RR, Siddiq, A *et al.* (2007) Harnessing Hypoxic-Adaptation to Prevent, Treat, and Repair Stroke. *J. Mol. Med.* **85(12)**, 1331-1338.

Siddiq, A, Aminova, L, and Ratan, RR (2007) Hypoxia Inducible Factor Prolyl 4 Hydroxylase Enzymes: Center Stage in the Battle Against Hypoxia, Metabolic Compromise and Oxidative Stress. *Neurochem. Res.* **32(4-5)**, 931-946.

Strathmann, FG, Wang, X, Mayer-Pröschel, M (2007) Identification of Two Novel Glial-Restricted Cell Populations in the Embryonic Telencephalon Arising From Unique Origins. *BMC Dev. Biol.* **7**, 33.

## Appendix IV

### Patents Resulting from Spinal Cord Injury Research Board-Funded Projects

**C019772 Burke/Cornell Medical Research Institute (CORE Project)**

Project Title: Center of Research Excellence - “A Novel Multimodality Approach to Treating Spinal Cord Injury.”

60/933,366 Compounds for Enhancing p21 Expression and Methods of Use Thereof

60/963,558 ATF4 Inhibitors and Their Use for Neural Protection, Repair, Regeneration, and Plasticity

11/831,416 System and Method to Enable Training a Machine Learning Network in the Presence of Weak or Absent Training Exemplars

**Appendix V**

**Presentation by Rajiv Ratan, M.D., Ph.D., Burke Medical Center,  
Weill Medical College of Cornell University  
Director, Center of Research Excellence in Spinal Cord Injury  
to the New York State Spinal Cord Injury Research Board  
January 25, 2007**