Annual Report
January 1, 2011 to December 31, 2011
NEW YORK STATE SPINAL CORD INJURY RESEARCH BOARD
Roster of Members
As of December 31, 2011

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

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

Blair Calancie, Ph.D.*
Upstate Medical University

Jeffrey D. Ehmann

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

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

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

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

Paul Richter
Spinal Cord Society

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

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

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

* appointed during 2011
New York State Department of Health Staff  
Wadsworth Center  
Extramural Grants Administration

Bonnie Jo Brautigam  
Executive Secretary to the Board and Director

Teresa K. Ascienzo  
Associate Accountant

Lani Rafferty  
Health Program Administrator 2

Mary Rogers Ryther  
Health Program Administrator 1

Nora Prall  
Administrative Aide
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I. INTRODUCTION

Spinal cord injury (SCI) used to be thought of as incurable. Significantly, the basic science carried out by researchers in this field, much of it in New York State, has served as an important stimulus for the clinical trials now underway in fields as diverse as neuro-rehabilitation, axon growth, cell biology and robotics. Although it is not yet possible to reliably repair the human spinal cord, there are treatments that improve the lives of SCI patients, and continued scientific explorations offer hope for doing more.

The Board appreciates the opportunity to serve the citizens of New York State by focusing on this important public health problem while stimulating economic growth through discovery. The Board looks forward to additional financial support for such highly meritorious SCI research in the coming years.

II. BACKGROUND

SCI is the second most common cause of paralysis. Each year, approximately 900 New York residents suffer traumatic spinal cord injuries (SCI), joining the nearly 1 in 50 people living in the United States with paralysis – approximately 6 million people. The personal and economic costs to these persons, their families and society are immense.

SCI results in a sudden change in the quality of life for those affected. Injuries can be caused by falling down stairs, from vehicle, diving or sports accidents, or from violent acts. Injuries to the spine near the head can result in quadriplegia, with the loss of motor control, sensation and function of the arms, legs, bowel, bladder, chest, abdomen and diaphragm. Injuries to the lower spine can result in loss of sensation and movement in the lower body, and loss of bowel and bladder control. Both types of injuries can result in constant pain.

The economic costs of SCI are great. In addition to medical care and loss of productivity, those with SCI incur significant costs for home and vehicle modifications, equipment purchase, medications and personal assistance services. The Institute of Medicine of the

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1. Christopher and Dana Reeve Foundation Survey, funded by a Cooperative Agreement with the Centers for Disease Control and Prevention
2. New York State Department of Health, Bureau of Injury Prevention, data from 2006-2008
National Academies reported that first year costs for an individual with SCI range from approximately $10,000 to $700,000, with annual costs thereafter ranging from approximately $14,000 to $122,000.\(^3\)

The New York State Spinal Cord Injury Research Board (SCIRB or Board) was created in 1998 to oversee and support proposals from leading New York State researchers in their efforts to find a cure for SCI. To fund this research, the Spinal Cord Injury Research Trust Fund (Trust Fund) was established, financed primarily by surcharges on moving traffic violations. Automobile accidents are the second leading cause of SCI in New York,\(^2\) after falls. The Board and Trust Fund were authorized by Title IV (Sections 250 through 251) to Article 2 of the Public Health Law and Section 99-f to Article 6 of the State Finance Law. The Board’s enabling legislation can be found at [http://www.wadsworth.org/extramural/spinalcord](http://www.wadsworth.org/extramural/spinalcord).

The Board was first convened in August 1999. The Board is responsible for advising the Commissioner of Health regarding the oversight of a program to support research proposals from leading New York State researchers in their efforts to find a cure for SCI, financed by the Trust Fund. The Board is required to report annually to the Governor and Legislature on its grant-related activities, the status of supported research and on the Trust Fund.\(^4\)

New York’s investment in SCI research has stimulated millions of dollars in additional funding for New York State researchers from sources such as the National Institutes of Health, the Department of Veterans’ Affairs, the Craig H. Neilsen Foundation, the Christopher and Dana Reeve Foundation and the Department of Defense, among others.\(^5\) The number of National Institutes of Health (NIH)-funded SCI research awards made to New York State researchers grew from 9 in 1998 to 21 in 2011.\(^6\) At least 18 spinal cord injury-related patent applications have been filed by New York State researchers since 2001.\(^7\) The scientific advancements of New York State’s research community lead to a better quality of life for its injured citizens and their families.

With over a decade of support from this program, New York State researchers are entrenched in ground-breaking SCI research. Researchers here made significant accomplishments in 2011 to better understand basic biological processes that occur in SCI, the mechanisms associated with the repair of the spinal cord and to translate those findings to clinical applications.


\(^4\) This report was prepared by the New York State Department of Health. Since there were no Board meetings in 2011, the Board has not approved the report.

\(^5\) As reported by SCIRB-funded contractors to the Chair of the Board in 2010.

\(^6\) National Institutes of Health, Research Portfolio Online Reporting Tools, search limited to “spinal cord injury.”

\(^7\) United States Trade and Patent Office on-line search, search limited to “spinal cord injury.”
III. BOARD ORGANIZATION AND MEMBERSHIP

The Board’s membership is comprised of 13 members appointed by the Governor and legislative leaders (see page iii). The composition of the Board’s current 12 members is approximately 40 percent basic science researchers, 25 percent clinicians and surgeons and 35 percent spinal cord-injured persons or advocates. Members serve four-year terms. One Board seat was vacant as of December 31, 2011. Brief biographies of each member can be found at http://www.wadsworth.org/extramural/spinalcord.

IV. BOARD OPERATIONS

Meetings

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

There were no Board meetings held in 2011.

Bylaws

No changes were made to the Board’s bylaws in 2011. The bylaws can be found at http://www.wadsworth.org/extramural/spinalcord and in Appendix II of this report.

V. PROGRAM FUNDS

Through December 31, 2011, deposits to the Trust Fund totaled $78.4 million. Interest on unexpended funds rose to almost $5.3 million, for a total of $83.7 million since the inception of the Trust Fund.

Cash disbursements from the Trust Fund include: payments for research contracts ($59.3 million); payments for peer-review and strategic planning contracts ($2.6 million); and administrative costs ($3.7 million) over the life of the Trust Fund.

VI. MAJOR ACTIVITIES OF THE BOARD AND PROGRAM

The 2011 Budget did not provide funding for new research projects, but did provide funding to continue contracts executed prior to April 1, 2010. Many important and exciting results have stemmed from that work. The remainder of this report addresses those activities.
**Presentations, Publications and Patents Resulting From SCIRB-Funded Research**

During 2011, investigators reported their findings in 20 scientific journal articles and made 11 presentations regarding SCIRB-funded projects at national and international meetings, symposia and other venues (Appendix III).

**Research Projects and Accomplishments**

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

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


The objectives of this project were to examine the possibility of re-establishing the functional synaptic connections to individual motoneurons throughout the injury region after lesion and contusion injuries. To investigate whether treatment would establish functional connections around or through the lesion, the researchers completed electrophysiological, tracing and behavioral experiments using a hemisection model of SCI in adult rats. Experiments using a contusion model of injury identified the cellular and molecular mechanisms responsible for the reduced transmission of nerve impulses through surviving fibers across from the injury site.

Decreased excitability, increased rheobase to trigger action potentials, pathological changes in the distribution of Nav1.6 Na-channels, and the demyelination of contralateral rubrospinal tract axons are likely responsible for the decreased conduction of nerve impulses after hemisection and thus may provide novel targets for strategies to improve function following incomplete SCI.

After lateral hemisection, researchers found that the monosynaptic responses were abolished. They were able to achieve the re-establishment of functional innervation of lumbar motoneurons by treating adult rats with the following agents: 1) anti-Nogo-A antibodies to neutralize the growth-inhibitor Nogo-A; 2) Neurotrophin-3 (NT-3) via engineered fibroblasts to promote neuron survival and plasticity; and 3) NMDA-receptor 2d (NR2D) subunit via an HSV-1 amplicon vector to elevate NMDA receptor function thereby enhancing synaptic plasticity and promoting the effects of NT3. The combined treatment also resulted in better motor function in the absence of adverse effects (i.e., pain arising from the treatment). Together, these results suggest that the combination of Nogo-Ab+NT3+NR2d is safe and can produce a functional “detour” around the lesion in a laterally hemisected spinal cord. This novel treatment may help to improve function of the damaged spinal cord.

To begin studies using a contusion model, a more realistic model of SCI, several control experiments were conducted and physiological outcomes between hemisection and contusion SCI were compared. Future studies should further examine a contusion model of SCI, and whether combination treatment would induce recovery of function after contusion injury.

The investigators previously showed that elevation of the molecule cyclic adenosine monophosphate (cAMP) will promote nerve regeneration within the environment of the adult brain and spinal cord. cAMP increases the levels of the enzyme Arginase, and Arginase is necessary for the cAMP effects in animal models of SCI.

However, the investigators recently found that if cAMP is continuously elevated, such as with continuous delivery of the drug Rolipram, the system becomes desensitized, the levels of Arginase drop and the nerves stop regenerating. Consequently, they proposed that intermittent increases rather than continuous elevation of cAMP will be more effective in promoting nerve regeneration. After characterizing the time course of desensitization in more detail, they have designed an intermittent treatment schedule that will optimize the cAMP effect on nerve regeneration.

The proposed intermittent Rolipram treatment – five days on, three days off, and another five days on – successfully promoted the regeneration of damaged axons following optic nerve injury. A time course of Arginase levels at each time point during treatment is being developed.

Furthermore, a form of the enzyme that synthesizes cAMP, soluble adenylyl cyclase, or sAC, is being characterized. This form of the enzyme is distributed throughout the cytosol of the nerve cell rather than being tethered to the membrane like other forms of the enzyme. The researchers showed that this enzyme is expressed in nerve cells, and that the ability of the drug brain-derived neurotrophic factor (BDNF) to allow nerve cells to grow in an inhibitory environment is dependent on sAC activity. Also, eliminating sAC from nerve cells shows that BDNF has no effect. Finally, the research has shown, preliminarily, that if the levels of sAC are increased in the nerves of the eye, the optic nerve will regenerate after it is injured.

Together with collaborators, the researchers screened a small molecule library to identify novel modulators of sAC activity. Using an *in vitro* cyclase assay, a number of potential activators and new inhibitors of sAC have been identified; whether these molecules have efficacy in cellular systems and whether they are specific for sAC is being determined. Once that has been established, their ability to allow nerves to grow in an inhibitory environment and to promote nerve regeneration in animal models of injury will be tested.


Most spinal lesions occur in young and otherwise healthy individuals and substantially impair ambulation, resulting in devastating effects on quality of life. Restoring locomotion after damage to the spinal cord is an enormously challenging problem, because axons of the damaged neurons do not regenerate spontaneously. Body weight unloading and manual assistance of the legs has been used by therapists as a means of rehabilitation of walking in people with SCI. Body-weight-supported treadmill training (BWSTT) is a therapeutic approach in which a person with SCI steps on a motorized treadmill while a portion of body weight is removed through an upper body harness.
There is a fundamental knowledge gap regarding the neural mechanisms underlying restoration of locomotion with BWSTT. The main objectives of this project are to determine the neural mechanisms underlying locomotion restoration following BWSTT, and to better understand spinal neural reorganization related to restoration of walking in people with chronic (greater than 2 year post injury) motor incomplete SCI.

Eight people with SCI have enrolled in the study. Six have completed all tests and have received 60 sessions of locomotor training. Two patients currently are receiving locomotor training, and will be re-tested. Approximately 60 experiments have been conducted in SCI subjects and 40 experiments in uninjured control subjects. Based on preliminary analysis of data, the investigators found that the injured human spinal cord has the capacity to reorganize itself, promoting physiological muscle activation patterns during assisted stepping. Spinal reflexes changed during assisted stepping, even in patients who had a complete SCI absent of voluntary movement and sensation in the legs. It remains to be determined to what extent restoration of walking after locomotor training is related to reorganization of spinal neuronal networks in people who have SCI but are capable of ambulation with assistive devices.

Over the next year, eight more participants will be recruited for the study and electrophysiological tests before and after locomotor training will be conducted. The next step is to investigate the reorganization of brain neuronal pathways that are responsible for movement. Based on these findings, the investigator plans to develop a randomized clinical trial for rehabilitation interventions that promote restoration of motor function.


This project is focused on devising a rational approach to identify the best cell source and cell population for SCI repair, and to characterize the behavioral outcome of the graft cells and the injury site in order to optimize recovery strategies.

Dr. Mayer-Pröschel’s laboratory has discovered a cell population that can be derived from embryonic spinal cords and induced to differentiate into two types of astrocytes in vitro. The transplantation of these cells into an injury model demonstrated for the first time that it is critical to use an appropriate cell type in the right context to achieve functional recovery. These initial exciting results opened up a number of additional questions, which were the focus of this project: (i) what cellular processes are associated with functional recovery; (ii) can functional recovery only be achieved if the transplanted cells are derived from the same regions (i.e., the spinal cord); (iii) is it necessary to pre differentiate progenitor cells into astrocytes to achieve functional recovery; and (iv) is it critical to derive the graft cells from embryonic tissue or can recovery also be achieved by using postnatal cells?

The experiments showed that one mechanism by which the transplanted cells contribute to recovery involves the secretion of neuroprotective agents, some of which are newly discovered. The transplantation of cells associated with functional recovery leads to recruitment of myelinating cells to the lesion and with a modulation of inflammation. The investigators determined that functional recovery is not dependent on using graft cells from the same region (i.e., spinal cord), since cells isolated from the cortex and differentiated into astrocytes also conferred functional recovery. Finally, experiments conducted show that the
use of cells that are embryonic in origin is a major critical factor for conferring functional recovery.

Innovative, Developmental and Exploratory Activities (IDEA) Awards

C023680, Jun Yan, Ph.D., Regenerative Research Foundation, "Human Neural Stem Cell Cultures From Adult Spinal Cord," October 1, 2008 – September 30, 2011; $360,000.

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

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

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

The investigators have optimized a full set of procedures for processing and culturing adult human spinal cord tissue that can be used by other researchers moving into this field. Many unique features of the adult human spinal cord organotypic cultures made it a suitable model for studying SCI and the reactions by the endogenous neural stem cells/neural precursor cells.

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

When the spinal cord is injured, damaged or cut axons do not regrow their axonal processes. This failure to establish appropriate synaptic connections with their target cells results in the functional deficits associated with SCI. It is generally accepted that environmental conditions at the injury site prevent axon regrowth, but the specific molecules at the injury site responsible and the mechanisms by which these molecules prevent regrowth is not well understood. Among the many molecules expressed at injury sites are the chondroitin sulfate
proteoglycans (CSPGs). These extracellular and cell-associated molecules inhibit axon regeneration. The goal of this project is to understand the mechanisms by which CSPGs prevent axon regeneration.

The investigators have identified a novel signaling pathway in neurons activated by CSPGs and a new target for therapeutic interventions designed to promote axon regrowth after SCI. Using growth inhibition by the neuron-glial antigen 2 (NG2) proteoglycan as a model, they showed that NG2 activates a cellular signaling complex known as the Par complex and this activation is both necessary and sufficient to inhibit axon growth in tissue culture. Activation of the Par complex leads to the inappropriate activation of a small molecule known as Rac1. Rac1 regulates the dynamic actin motor required for axon growth. Thus, extracellular proteoglycans such as NG2 activate the Par complex, and this in turn disrupts the machinery necessary for axon growth.


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

The goals of this project are to develop a new model of bladder-sphincter dyssynergia in the rat and to identify spinal cord transection-induced changes in the intrinsic electrical properties of EUS motoneurons that may contribute to bladder-sphincter dyssynergia. Identification of an EUS motoneuron-based mechanism will provide a new model for understanding the cause of bladder-sphincter dyssynergia and for the development of effective new therapies.

After establishing the basic experimental rat model in the laboratory, studies characterizing bladder-sphincter reflexes in spinally intact and transected adult rats were completed. The investigators quantified three distinct phases of EUS activation associated with urine discharge: 1) EUS Guarding Reflex - increasing tonic EUS activity during bladder filling; 2) EUS Bursting - alternating synchronized EUS activation and relaxation with voiding at the peak of bladder contraction; and 3) EUS Sustained Activity - sustained tonic EUS activity following voiding. The EUS guarding reflex was enhanced in rats with midthoracic spinal cord transection while both EUS bursting and EUS sustained activity were markedly reduced. Also, the researchers observed a marked increase in EUS motor unit spike frequency during the EUS guarding reflex in transected rats, compared to intact rats, which likely contributed to the enhanced EUS guarding reflex and bladder-sphincter dyssynergia. Further, inhibiting the EUS guarding reflex with intrathecal administration of the muscle relaxant baclofen (0.25 g) decreased bladder-sphincter dyssynergia and improved voiding. Studies to elucidate the mechanisms underlying EUS bursting and EUS sustained activity are ongoing.

Pathological changes in the peripheral nerves and muscles following SCI have been reported in several human and animal studies. However, the mechanisms for these changes are not well understood. The focus of this project is to identify mechanisms that can mediate negative changes in peripheral nerves and muscles following SCI. The research focused on beneficial effects of transspinal magnetic and electrical stimulations on functional recovery after SCI, using both a hemisection model and a contusion model of SCI in mice.

Magnetic stimulation (MS) with a commercially available instrument, MagStim, was used to apply a magnetic electrode over the injured area of the spinal cord. MS was applied either separately, or in combination with acrobatic exercise. Those animals exposed to both MS and acrobatic exercise demonstrated the best progress in functional recovery.

During this study, the investigators developed a new type of electrical stimulation of the spinal cord, which they call trans-spinal Direct Current Stimulation (tsDC). The stimulation to the spinal cord was delivered with two electrodes. While one electrode was placed over the vertebral column, the second one was located on the abdomen. The activity of spinal neurons and the efficiency of pathways regulating muscle contraction were remarkably improved by the application of tsDC. The effect was enhanced further by simultaneous activation of the motor cortex.

In investigating the processes involved in SCI and recovery-aimed treatments, the role of molecules which modulate the activity of spinal cord neurons and stimulate neuronal regeneration cannot be ignored. Following injury, excessive amounts of glutamate are released. Glutamate is a major excitatory neurotransmitter in the spinal cord, and contributes to excitotoxicity and secondary lesions. Following application of either MS or tsDC, glutamate was significantly increased. This finding may give an insight of how magnetic and electrical stimulation influence the tissue, and indicates that the mechanism of glutamate changes can be considered as a potential target for treatment. The researchers concluded that application of magnetic or electrical stimulation exerts a neuro-protective effect and promotes spinal recovery.

The results of the study provide support and the basis for the use of trans-spinal magnetic and/or electrical stimulation as a rehabilitative tool for patients with SCI. Both methods of stimulation can be easily applied in rehabilitation centers in combination with physical therapy to maximize functional recovery.


People with incomplete SCI often suffer from movement problems, even after completing conventional therapy. Common movement problems such as spasticity and weak muscle control after SCI are the results of changes in brain-spinal cord pathways and spinal reflex pathways. Thus, reducing abnormalities in the activity of these pathways may lead to better movement recovery. The goal of this project is to evaluate electromyogram/electroencephalogram (EMG/EEG) training as a new therapeutic approach and to investigate whether the successful muscle response training leads to improvement of gait in people with SCI.
Building on decades of successful animal research by others, the researchers developed a unique EMG/EEG muscle response training protocol for people to change the activity of brain-spinal cord and spinal reflex pathways. This project includes two muscle response training studies: spinal reflex training and brain stimulation training. Twenty-six subjects have been enrolled in these studies.

The results show that people with SCI are able to learn to change the muscle response after the training. In people who successfully completed the training, gait clearly improves - not only does the walking speed improve, but the step rhythm and muscle activation patterns become more normal. Many subjects noted reduced spasticity and required less effort in walking. Also, examination of brain-wave activity has indicated some possible links between brain-wave activity and muscle response training, which leads to better function recovery.

With the success of this project, a five-year research grant from the National Institutes of Health (NIH) has been obtained, which will help researchers further examine the therapeutic effects of their training approach in improving gait after SCI. Multi-center trials for evaluating the therapeutic effects of this approach on a larger scale are planned, with a goal of making this procedure available at regular hospitals or therapy clinics as an option for therapeutic treatment after SCI.

**Mentored Scientist Development Awards**

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

SCI is a devastating event with few victims recovering to their normal functionality. Most of those who sustain a SCI are paralyzed either from the waist or the neck down, depending on the injury. Acute interventions which can quickly prevent irreversibility of the injury have yet to be discovered.

In this project, the researchers used direct visualization of the immune cells of injured tissue from acute to chronic stage. Using a microscope system called multi-photon laser scanning microscopy, mouse models of SCI and inflammation were explored. This system enables imaging of tissue deeper than other modalities and therefore allows for direct imaging of live animals right as the injury occurs. In most research models, this acute phase is poorly understood and this imaging offers a rare opportunity to study the critical time window when potential therapies to reverse the effects of injury can intervene.

In earlier work, the investigators found that microglia, immune cells inside the spinal cord tissue, are the first protectors of injury. They found that as time passes and the injury becomes more inflamed, other immune cells from the blood begin to play an important role in exacerbating the injury of the spinal cord/brain tissue.

Using the multi-photon laser scanning microscopy, the researchers examined CXCR6, a protein molecule expressed by immune cells and which enters the spinal cord. They found that injured tissues can beckon cells that express CXCR6 by sending out the protein molecule CXCL16, which is the binding partner of CXCR6. They also began examining another molecule involved in CNS injury, myristoylated alanine-rich C kinase substrate, or MARCKS, which is important for immune cells inside the brain to protect the injured tissue.
Using this system, an unlimited number of potential molecular targets can be examined to help identify potential therapeutic intervention. The researchers will continue to identify such molecular targets in pursuit of discovery of therapeutic modalities to cure SCI.

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

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

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

The researchers have successfully measured the glycocalyx layer of capillaries in spinal cord tissue before and after SCI. The measurements showed a decrease in the thickness of the layer, along with reduction of flow, showing that the loss of the glycocalyx layer was an early event after the injury, preceding the onset of the development of secondary injury. At 24 hours post injury, peri-traumatic regions were virtually devoid of fast-flowing capillaries. Therefore, soon after the initial SCI, the reduction of both the glycocalyx layer and capillary flow rate occur. Blood vessels also become leaky, disrupting the proper condition of brain tissue homeostasis. Inflammatory response was observed in small populations of large blood vessels. The investigator’s attempt to remedy the loss of glycocalyx with pluronic acid as a substitute lubricant made little improvement on functional recovery. The tissue oxygen level supplied by a single capillary was measured, to confirm that the reduction of capillary blood flow leads to the shortage of oxygen supply.

The investigators also performed studies which showed the importance of the coenzyme adenosine triphosphate (ATP) to inflammatory response. Inflammatory response worsens the degree of injury after the initial impact to the spinal cord, and prevents axonal and functional regeneration. Using a transgenic model, the investigators blocked ATP release from astrocytes, which deletes connexin expression in astrocytes, and results in the reduction of extracellular ATP levels as well as the reduction of inflammatory response and improved functional recovery.
Program Projects Award


The goal of this research is to improve functional recovery after SCI through the development of novel compounds that have the potential to reduce axonal loss and improve the quality of lives of SCI patients. These compounds are designed to increase axonal levels of the coenzyme NAD, a compound that has recently been recognized to prevent axon degeneration after insults such as axonal compression injury.

This project focuses on three strategies to achieve this goal: 1) development of novel NAD precursors that rapidly enter neurons and increase neuronal NAD levels; 2) identification of intracellular signaling pathways which mediate protective effects of NAD to clarify novel biosynthetic entry points for NAD precursors and help guide the design of novel therapeutics; and 3) testing these compounds in animal models of SCI to determine which compounds are likely to be valuable candidates to advance toward clinical trials.

Significant progress has been made. A number of NAD enhancing compounds that exert remarkable effects on neuronal survival and axonal preservation have been developed. Novel mechanisms of NAD utilization which point to new approaches for enhancing the use of NAD-augmenting compounds have been identified.

With dosing and administration studies well underway, studies in animals to test these molecules have been initiated to substantiate the potential power of these compounds for the treatment of SCI. Together, these studies will provide the crucial preclinical data needed for an investigational new drug application needed for FDA-approved clinical trials.

VII. CONCLUSION

This very successful SCI research program has enabled highly qualified New York State researchers to develop treatments, alleviate pain associated with SCI, restore function and to search for a cure for SCI.
Appendix I

Laws of New York State


1. A spinal cord injury research board is hereby created within the department for the purpose of administering spinal cord injury research projects and administering the spinal cord injury research trust fund created pursuant to section ninety-nine-f of the state finance law. The purpose of research projects administered by the board shall be neurological research towards a cure for such injuries and their effects. The members of the spinal cord injury research board shall include but not be limited to representatives of the following fields: neuroscience, neurology, neuro-surgery, neuro-pharmacology, and spinal cord rehabilitative medicine. The board shall be composed of thirteen members, seven of whom shall be appointed by the governor, two of whom shall be appointed by the temporary president of the senate, two of whom shall be appointed by the speaker of the assembly, one of whom shall be appointed by the minority leader of the senate, and one of whom shall be appointed by the minority leader of the assembly.

2. Board members shall be reimbursed for ordinary travel expenses, including meals and lodging, incurred in the performance of duties pursuant to section two hundred fifty-one of this title.

3. The terms of board members shall be four years commencing January first, nineteen hundred ninety-nine.

4. At the end of a term, a member shall continue to serve until a successor is appointed. A member who is appointed after a term has begun shall serve the rest of the term and until a successor is appointed. A member who serves two consecutive full four year terms shall not be eligible for reappointment for four years after completion of those terms.

5. A majority of the full authorized membership of the board shall constitute a quorum.

6. One member of the board shall be chosen by the governor to serve as chairperson.

7. Meetings of the board shall be held at least twice a year but may be held more frequently as deemed necessary, subject to call by the chairman or by request of a majority of the board members. Board meetings shall concern, among other things, policy matters relating to spinal cord injury research projects and programs, research progress reports, and other matters necessary to carry out the intent of this title.

8. Members of the board shall be indemnified pursuant to section seventeen of the public officers law.
**Title IV, § 251. Powers and Duties.**

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

1. Formulate policies and procedures necessary to carry out the provisions of this title;

2. Solicit, receive, and review applications from public and private agencies and organizations and qualified research institutions for grants from the spinal cord injury research trust fund, created pursuant to section ninety-nine-f of the state finance law, to conduct research programs which focus on the treatment and cure of spinal cord injury. The board shall make recommendations to the commissioner, and the commissioner shall, in his or her discretion, grant approval of applications for grants from those applications recommended by the board.

3. Ensure that state funds, appropriated for spinal cord injury research are not diverted to any other use; and

4. Provide the governor and the legislature an annual report by January thirty-first of each year succeeding the year in which this title shall take effect setting forth the status of funds appropriated for spinal cord injury research and the progress of the Board in terms of the results of its spinal cord injury research efforts.

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

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

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

** This section was not codified to law; however, the State Finance Law, as amended by Chapter 612 of the Laws of 1999, currently reads as follows:
State Finance Law, Article 6

1. There is hereby established in the joint custody of the state comptroller and the commissioner of taxation and finance a special revenue fund to be known as the “spinal cord injury research trust fund.”

2. The fund shall consist of all monies appropriated for its purpose, all monies required by this section or any other provision of law to be paid into or credited to such fund, and monies in an amount not to exceed eight million five hundred thousand dollars collected by the mandatory surcharges imposed pursuant to subdivision one of section eighteen hundred nine of the vehicle and traffic law. Nothing contained herein shall prevent the department of health from receiving grants, gifts or bequests for the purposes of the fund as defined in this section and depositing them into the fund according to law.

3. Monies of the fund, when allocated, shall be available for administrative costs of the spinal cord injury research board established pursuant to title four of article two of the public health law and for funding spinal cord injury research projects administered by such board.

4. Monies shall be payable from the fund on the audit and warrant of the state comptroller on vouchers approved and certified by the commissioner of health.
Appendix II

Bylaws of the Spinal Cord Injury Research Board

I. OFFICERS

1. The officers of the Spinal Cord Injury Research Board ("Board") shall be the Chair and Vice-Chair. The Chair is designated by the Governor. The Vice-Chair shall be selected by the Chair and shall serve for one year or until his or her successor has been selected.

2. The Chair may appoint a Board member to preside during the absence of the Chair and Vice-Chair from any meeting.

II. DUTIES

1. The officers of the Board shall perform the duties ordinarily associated with their respective offices.

2. The Chair shall be responsible for the general supervision of the work of the Board. The Chair shall represent the Board before the Governor, committees of the Legislature, or other public authorities, and may request any member or members to appear with him or her in his or her stead. The Chair shall preside at Board meetings.

3. The Vice-Chair, in the absence of the Chair, shall perform the duties of the Chair.

III. CODE OF ETHICS AND CONFLICT OF INTEREST

Section 1. Code of Ethics.
Members of the Board shall comply with Section 74 (Code of Ethics) of the Public Officers Law. No member of the Board should have any interest, financial or otherwise, direct or indirect, or engage in any business, transaction, or professional activity, or incur any obligation of any nature, which is in substantial conflict with the proper discharge of his or her duties as a Board member. Members should exercise their duties and responsibilities as Board members in the public interest of the inhabitants of the State, regardless of their affiliation with, or relationship to, any institution, organization, facility, agency, program, activity, category of provider, or interest group. The principles that should guide the conduct of Board members include, but are not limited to, the following:

a) A Board member should endeavor to pursue a course of conduct that shall not raise suspicion among the public that he or she is likely to be engaged in acts that are in violation of his or her trust as a Board member.

b) No Board member should permit his or her employment to impair his or her independence of judgment in the exercise of his or her duties as a Board member.
c) No Board member should disclose confidential information acquired by him or her in the course of his or her duties as a Board member, or by reason of his or her position as a Board member, nor use such information to further his or her personal interests.

d) No Board member should use, or attempt to use, his or her position as a Board member to secure unwarranted privileges or exemptions for himself or herself or others.

e) No Board member should engage in any transaction as a representative or agent of the State with any business entity in which he or she has a direct or indirect financial interest that might reasonably tend to conflict with the proper discharge of his or her duties as a Board member.

f) A Board member should not make personal investments in enterprises which may be directly involved in decisions to be made by him or her as a Board member or which shall otherwise create substantial conflict between his or her duty as a Board member to act in the public interest and his or her private interest.

g) To preserve the public trust, Board members are prohibited during the tenure of their appointment from applying for or receiving support from the Spinal Cord Injury Research Trust Fund under Section 251 of the Public Health Law, or from having any role or interest (other than routine professional and collegial interest in the success of their institution or department) in proposals submitted for consideration by, or in research or proposals supported by, the Spinal Cord Injury Research Trust Fund.

Section 2. Conflict of Interest – Applications and other Pending Matters.
This section applies both to activities of the full Board and its committees.

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

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

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

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

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

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

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

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

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

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

IV. EXECUTIVE SECRETARY

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

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

V. MEETINGS OF THE BOARD

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

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

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

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

e) Public Comment Period.
At least some portion of every regular Board meeting shall be set aside for public comment.

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

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

a) Standing Committees
There shall be the following Standing Committee:

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

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

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

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

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

VII. PROPOSAL REVIEW PROCESS

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

VIII. OFFICE OF THE BOARD

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

IX. AMENDMENT OF BYLAWS

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

Publications and Presentations Reported in 2011
Resulting From Spinal Cord Injury Research Board-Funded Projects

C022058 Stony Brook University, SUNY
Project Title: Neurotrophins and Function of the Injured Spinal Cord


C022062 Nathan S. Kline Institute for Psychiatric Research
Project Title: Aquaporin-4 Water Channels in Spinal Cord Injury


C023681 Stony Brook University, SUNY
Project Title: Functions of Atypical Protein Kinase C in Axon Regeneration
C023683
Stony Brook University, SUNY

Project Title: Bladder-Sphincter Dyssynergia: Role of Intrinsic Motoneuron Properties


C023684
College of Staten Island, City University of New York (CUNY)

Project Title: The Combined Effect of Acrobatic and Magnetic Stimulation on SCI


C023685
Helen Hayes Hospital

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

Thompson AK. “Operant Conditioning of EMG Evoked Responses in Health and Disease.” Presentation, Department of Biomedical Sciences, School of Public Health, University at Albany and Wadsworth Center, Albany, New York, March 31, 2011.


Hunter College, CUNY
Project Title: Targeting Soluble AC for the Recovery of Spinal Cord Injury


College of Staten Island, CUNY
Project Title: Mechanisms Underlying Locomotor Recovery After Step Training in SCI


C023691
University of Rochester
Project Title: Specific Astrocyte Subtypes for SCI Repair Without Allodynia


C023832
Weill Medical College of Cornell University
Project Title: Synthesis and Evaluation of NAD-Augmenting Agents for Spinal Cord Injury


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>BDNF</td>
<td>brain-derived neurotrophic factor</td>
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<tr>
<td>BWSTT</td>
<td>Body-weight-supported treadmill training</td>
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<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
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<tr>
<td>CSPGs</td>
<td>chondroitin sulfate proteoglycans</td>
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<tr>
<td>CART</td>
<td>Collaborations to Accelerate Research Translation</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CSPG</td>
<td>chondroitin sulfate proteoglycans</td>
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<tr>
<td>CUNY</td>
<td>City University of New York</td>
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<tr>
<td>EEG</td>
<td>electroencephalogram</td>
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<td>EF</td>
<td>electric field</td>
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<tr>
<td>EMG</td>
<td>electromyogram</td>
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<tr>
<td>EUS</td>
<td>external urethral sphincter</td>
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<tr>
<td>GDNF</td>
<td>glial-derived neurotrophic factor</td>
</tr>
<tr>
<td>IDEA</td>
<td>Innovative, Developmental or Exploratory Activities</td>
</tr>
<tr>
<td>MS</td>
<td>magnetic stimulation</td>
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<tr>
<td>MARCKS</td>
<td>myristoylated alanine-rich C kinase substrate</td>
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<tr>
<td>NAD</td>
<td>nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NG2</td>
<td>neuron-glial antigen 2</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>sAC</td>
<td>soluble adenylyl cyclase</td>
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<tr>
<td>SCI</td>
<td>spinal cord injury</td>
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<tr>
<td>SCIRB</td>
<td>Spinal Cord Injury Research Board</td>
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<tr>
<td>SUNY</td>
<td>State University of New York</td>
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<tr>
<td>tsDC</td>
<td>trans-spinal Direct Current Stimulation</td>
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