Innovative Research *for a* Better Life

PVA grants advance the understanding of spinal-cord injury and diseases.

by Elinor Tucker, MSW

What happens at the cell level when a spinal-cord injury or disease (SCI/D) occurs? What factors obstruct recovery—and which ones promote it? Understanding these basic processes is the key to improving treatments for people with paralysis and moving forward to find a cure.

The PVA Research Foundation recently awarded 13 grants, totaling $1.56 million, devoted to answering these questions. By providing seed money for innovative research, development of assistive devices, and post-doctoral fellowships, the foundation plays an important role in advancing the science needed to understand and treat SCI/D.

The grants also invest in the future of medical science by supporting fellowships in spinal-cord research. These enable young scientists to pursue specialization in this field. Fellowship grants often come at a critical turning point in young researchers' careers, when they must choose a particular focus for their work. Frequently, fellowships lead to a lifetime research commitment, and we hope such a commitment will focus on SCI/D. In addition, fellowship pilot projects, funded by the Research Foundation, often can demonstrate sufficient success to enable them to secure more generous federal funding.

The foundation received 70 applications by its September 1, 2007, deadline, approved 16, and awarded 13. Among the 13 grants awarded, 5 are for basic science research, 5 are for clinical studies, and 3 are for fellowships. All promise to improve the lives of individuals with SCI/D.

Basic Science

Inflammation in Chronic SCI

Raymond J. Grill, PhD
University of Texas Health Science Center
Houston, Tex.
$143,556 (2 Years)

Traumatic SCI causes inflammation that destroys or permanently alters cord tissue for weeks after injury. Arachidonic acid ("AA") production/signaling is thought to be a potent contribution to this inflammatory response. Elements of AA-signaling influence a wide range of postinjury activities including scar formation, regeneration failure, and the formation of neuropathic pain. Previous studies indirectly indicate that elements of AA-signaling are fleeting following SCI, peaking within hours to days of injury; in chronic SCI (months to years postinjury) inflammation is thought to be greatly reduced. Thus, conventional wisdom suggests that while cord tissue does not get better, it also doesn't worsen. Dr. Grill's studies

Studies by Raymond Grill, PhD, of the University of Texas Health Science Center in Houston, suggest inflammation continues throughout the chronic phase of injury.

In Atlanta, Shawn Hochman, PhD, will try to determine the role of potentially "new" transmitters on locomotion.

have recently questioned that hypothesis. His current proposal suggests pathological events continue throughout the chronic phase of injury. If this is true, it presents novel targets for intervention to improve outcome in chronic SCI.

Discovery of Intrinsic Spinal Aminergic Circuits that Control Locomotion

Shawn Hochman, PhD
Emory University
Atlanta
$150,000 (2 Years)

Nerve cells produce a class of chemical transmitters called *monoamines*. These cells are not part of the spinal cord but affect it by adjusting spinal sensory, autonomic, and motor activity. Loss of these outside control systems, as can occur after SCI, undoubtedly contributes significantly to the abnormal spinal activity that emerges. Hence, one therapeutic objective is to provide monoamine-like drugs to replace lost control systems. This approach has been shown to facilitate activation of locomotor circuits.

Octopamine, phenylathylamine, tyramine, and tryptamine are related to the classical monoamine transmitters mentioned above and are synthesized from the same dietary precursor building-block amino acids. They are present in low concentrations and so are classified as "trace" amines (TAs). The seminal discovery in 2001 of a new family of receptors preferentially activated by TAs rekindled interest in these substances; but without an identifiable circuitry, the function of TAs remains speculative.

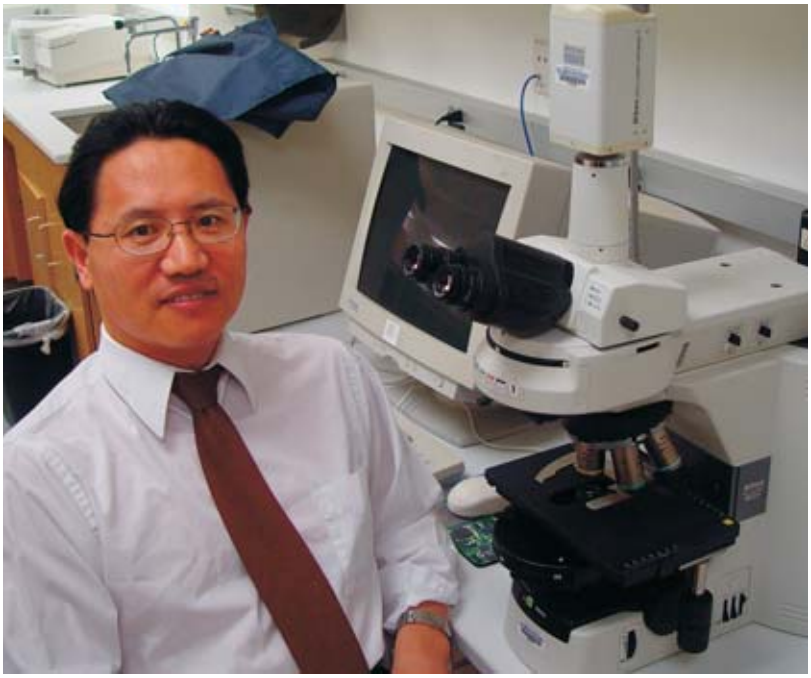
This project proposes to determine in detail the role of these potentially "new" transmitters on spinal-cord movement control.

Promoting Recovery in Spinal Cord Injury via RhoA Inhibition

Shuxin Li, MD, PhD
University of Texas Southwestern Medical Center
Dallas
$149,923 (2 Years)

Individuals with SCI experience axonal damage in the central nervous system (CNS) and often have persistent and severe functional losses. After injury, axonal disconnection and myelin-sheath damage in the spinal cord usually result in signal conduction failure. So far, the medical treatments to enhance recovery from neurological loss due to axonal damage are extremely limited because the severed axons do not grow back in an adult central nervous system (CNS).

This project's long-term goal is to illuminate the molecular and cellular mechanisms underlying CNS axon damage and growth failure and to develop effective strategies for recovering neurological deficits caused by axon and myelin damage. This principal investigator hypothesizes that activation of RhoA, a GTP-binding signal protein, is critical for restricting axon growth and for inducing cell death after a CNS axonal injury.



Shuxin Li, MD, PhD, believes certain drugs such as ibuprofen may lead to a successful treatment for people with SCI. His investigations are taking place at the University of Texas Southwestern Medical Center, in Dallas.

Thus, RhoA becomes an important therapeutic target. RhoA inactivation with non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (but not aspirin) may lead to a successful strategy for treating individuals with SCI in the near future.

Using Local Axonal Membrane Protein Synthesis to Improve Axonal Regeneration

Tanuja T. Merianda, PhD
Alfred I. duPont Hospital for Children / Nemours Children's Clinic
Wilmington, Del.
$150,000 (2 Years)

Axonal damage in SCI often results in permanent loss of sensory communication between the brain and its target tissues. Much effort has been directed at trying to coax spinal-cord axons into regenerating and restoring communication between these. Consequently, the investigator believes we need to explore additional cellular mechanisms that might help to improve regeneration.

The recent observation that injured axonal processes are capable of locally synthesizing new proteins raises the exciting possibility that this could provide an option to improve regeneration in the spinal cord. Dr. Merianda plans to test whether depleting two cellular substances (axonal amphoterin and NMP35 mRNAs) can be used to facilitate axonal regeneration. She will test this hypothesis by depleting these substances to determine the contribution of their locally synthesized proteins in regeneration. She will then increase the availability of those substances to determine if she can increase regeneration by regulation of the availability of axonally localized membrane protein mRNAs.

Two years ago, Dr. Merianda was chosen as the recipient of PVA's annual Fritz Krauth Memorial Fellowship, which is awarded to the highest-ranking fellowship candidate each year. Based on the outstanding results from her 2006 grant, she advanced to become a principal investigator—just the kind of success the foundation hopes to inspire. In recognition of her current achievement as the year's highest-ranking basic science researcher, the foundation's Board of Directors asked her to conduct her research in honor of Harley Thomas, a long-time PVA Health Policy analyst, who died in 2007.

After receiving PVA's Fritz Krauth Memorial Fellowship two years ago, Tanuja T. Merianda, PhD, went on to become a principal investigator.

Mouse Spinal Cord Anatomic Gene Expression Atlas

Ralph Puchalski, PhD
Allen Institute for Brain Science
Seattle
$75,000 (1 Year)

Ralph Puchalski, PhD, is working on an atlas that will not only facilitate ALS research but also support the entire spinal-cord research community.

The Rehabilitation Institute of Chicago is the site of research by Elizabeth Kay, PhD, who is examining functional outcomes for older adults with incomplete paraplegia resulting from nontraumatic SCI.

The spinal-cord research community lacks a genome-wide, publicly accessible database detailing gene expression at the cellular level for the mouse spinal cord. Investigators focused on particular diseases or disorders—including multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), or injury—typically resort to searching for the expression pattern of a particular gene in the published literature.

The Allen Institute recently completed the Allen Brain Atlas, a genome-wide mapping of gene expression for approximately 18,500 genes at cellular level. The current project proposes to create a similar high-resolution anatomic gene expression for the mouse spinal cord. The proposed atlas would feature publicly accessible images in a Web-based application with information released immediately. The atlas is designed for facilitating ALS research by the inclusion of two developmental time points and all segments of the cord, which facilitates a direct comparison between the time points and segments that manifest ALS and those that do not.

Creation of the atlas would support the entire spinal-cord research community and bring the public to a new level of awareness of spinal-cord research.

Development of a pain-assessment tool is the goal of a project by Sophia Chun, MD, in Long Beach, Calif. This would allow clinicians to distinguish between the types of SCI-related pain.

Clinical Applications

Translating the SCI Pain Classification into a New SCI Pain Assessment Tool

Sophia Chun, MD
Southern California Institute for Research and Education
Long Beach, Calif.
$150,000 (2 Years)

Pain is a common secondary complication among individuals with SCI/D, with prevalence estimates ranging from 77% to 81%. Individuals with SCI experience various types of pain that can limit daily activities and diminish quality of life. Accurate diagnosis of the specific type can lead to effective treatment and management. While many SCI pain classification schemes are available, these classification schemes have little clinical application.

The goal of this study is to develop a Spinal Cord Injury Pain Assessment Tool (SCI-PAT) that can be used by a wide range of healthcare professionals in the clinical setting to quickly and accurately diagnose the various types of pain. The development of the evidence-based, valid, and reliable SCI-PAT would offer clinicians a standardized tool to distinguish between the different types of SCI-related pain.

Proper pain diagnoses can lead to better treatment outcomes that improve quality of life for people with SCI.

Motor Outcomes in Older Adults with Non-traumatic Spinal Cord Injury

Elizabeth Kay, PhD
Rehabilitation Institute of Chicago
Chicago
$48,350 (1 Year)

The consequences of SCD are devastating and costly, whether traumatic (T) or nontraumatic (NT) in origin. The Model Spinal Cord Injury Sys-

tem has stimulated study of function after T-SCI but little is known about function after nontraumatic damage (NT-SCI) such as spinal-cord lesions due to disease, surgical complications, or congenital causes. The incidence of NT-SCI has been estimated to be 8 per 100,000 population per year in the U.S., with about 80% of new spinal-cord lesions occurring in adults over 40 being NT.

Few studies have examined outcomes for patients with NT-SCI, and these are limited by including too few subjects, longer lengths of stay in rehabilitation, use of an outdated method of injury classification, and the absence of functional information. This study will investigate functional outcomes for 65–74-year-olds with incomplete paraplegia from a NT-SCI when discharged from inpatient rehabilitation.

These study results will increase understanding of functional outcomes after NT-SCI that could be used to improve treatment, and as baseline data to determine the effectiveness of new treatments, assistive devices, and reimbursement policies that would further maximize function, independence, and quality of life.

Long Term Follow Up of Neuroprosthesis Users

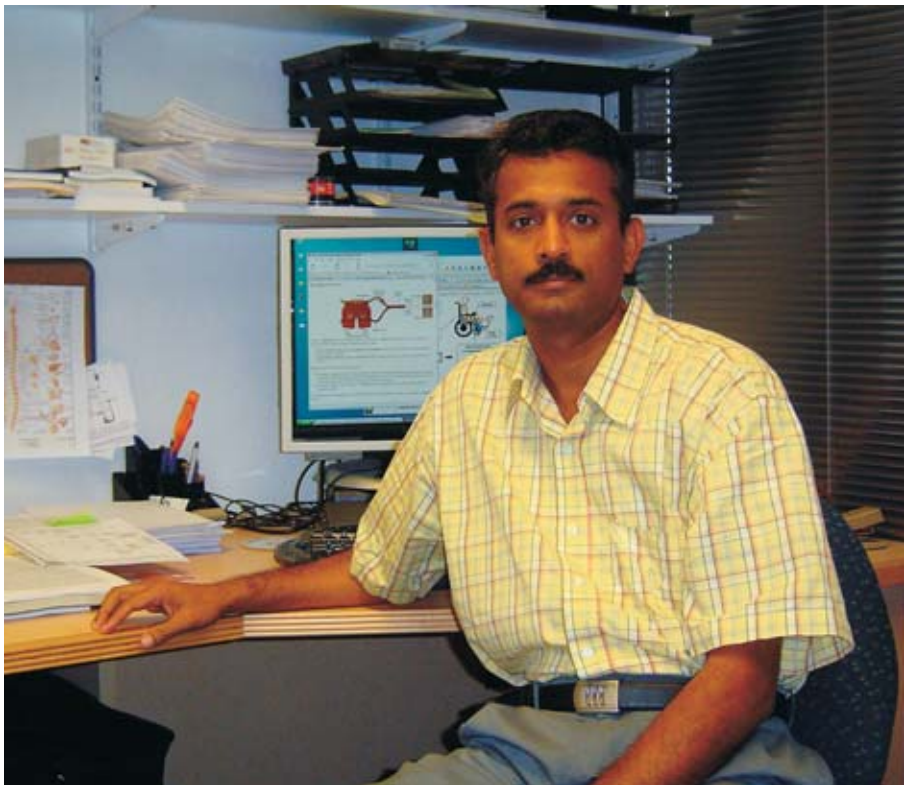
Kevin Lloyd Kilgore, PhD
The MetroHealth System
Cleveland
$149,991 (2 Years)

The loss of hand and arm function due to high-level SCI can severely restrict a person's ability to perform even simple activities such as eating and personal hygiene. Implanted neuroprostheses, which use functional electrical stimulation (FES) to activate paralyzed muscles, can provide these individuals with hand opening and closing, thus improving function and independence.

Implanted neuroprostheses that enable hand opening and closing improve function and independence. Kevin Kilgore, PhD, of The MetroHealth System in Cleveland, will perform long-term follow-up on people who have these devices.

Since the first implanted prostheses were introduced at the Cleveland FES Center in 1986, more than 250 people have received various generations of these systems. Because of the success of the implanted devices, subjects continue to use the neuroprosthesis in their daily lives well after the end of each funded study.

The purpose of this study is to perform quantitative long-term follow-up on these subjects and to provide them with continued technical support where necessary.

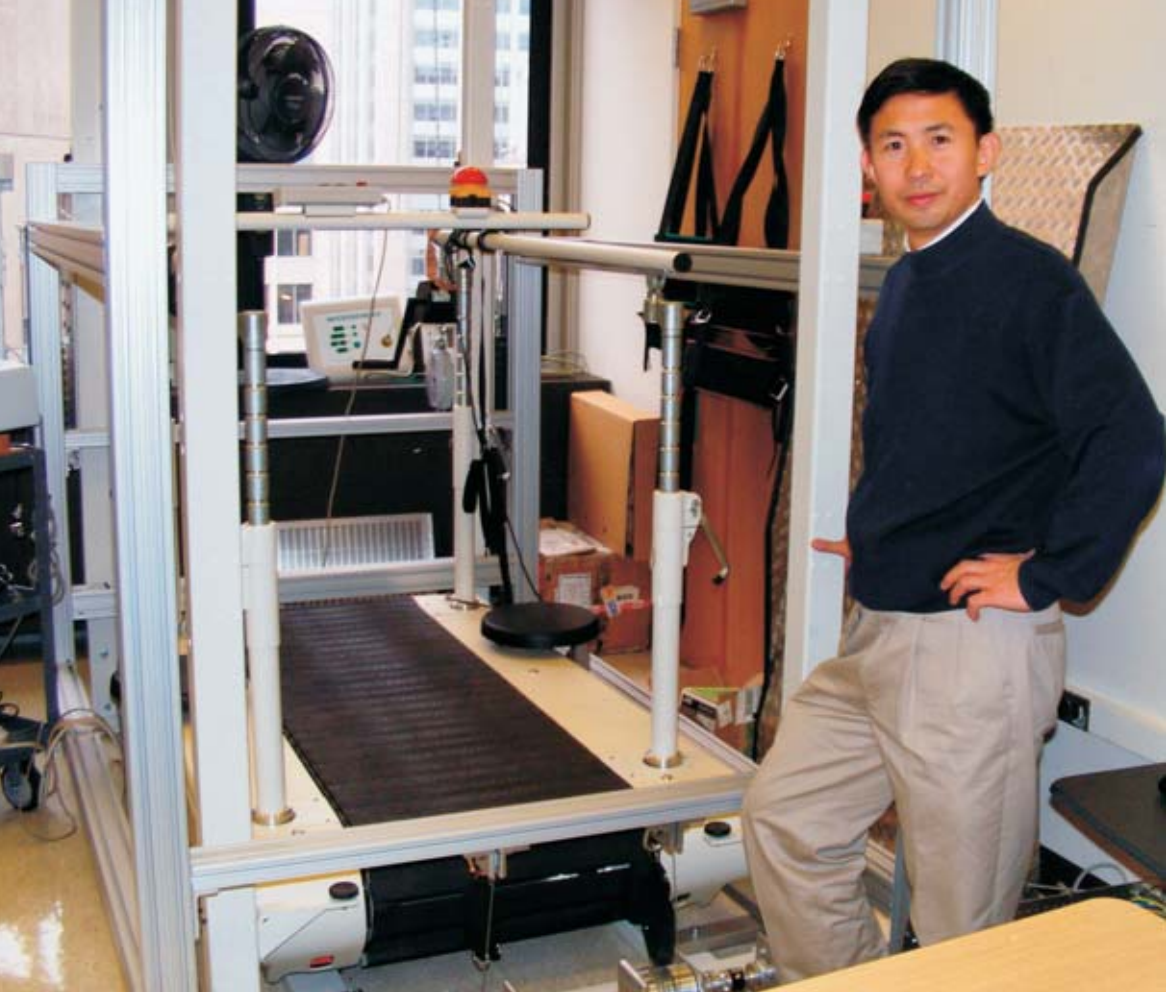


At Arizona State University in Tempe, Ariz., investigator Narayanan Krishnamurthi, PhD, will study the effects of exercise using electrical stimulation of leg muscles to help improve circulation and blood-pressure control.

Improving Orthostatic Tolerance after Spinal Cord Injury

Narayanan Krishnamurthi, PhD
Arizona State University
Tempe, Ariz.
$150,000 (2 Years)

For many of the approximately 250,000–400,000 people with SCI in the United States, the injury affects not only their ability to use their muscles and feel their limbs but also the body's ability to control heart rate and blood pressure. This condition can limit participation



Ming Wu, PhD, suggests adaptive resistance training might improve independent walking function in people with incomplete SCI. His two-year project is at the Rehabilitation Institute Research Corporation, in Chicago.

in rehabilitation programs and can have long-term health consequences.

In this project, the investigator will study the effects of long-term (12 weeks) use of an exercise program involving electrical stimulation of leg muscles to determine if it can help to improve circulation and blood-pressure control. This exercise training does not require expensive instruments, and it can be practiced at home after an initial, short training period. If successful, this technique can help accelerate progression through rehabilitation programs and could improve long-term health for people with SCI.

Improved Locomotion in Human SCI through Locomotor Adaptation

Ming Wu, PhD
Rehabilitation Institute Research Corporation
Chicago
$150,000 (2 Years)

While body-weight-supported treadmill training (BWSTT) has been shown to provide greater improvements in locomotor ability, motion function, and balance than conventional rehabilitation techniques, its effectiveness is likely to be improved by minimizing the amount of assistance provided and allowing independent walking practice.

This investigator hypothesizes that adaptive resistive training might improve independent walking function in people with incomplete SCI by adding adaptive resistance at targeted phases of walking during BWSTT in order to augment motor adaptation. Resistance or assistance load will be applied to the legs at the ankle and above the knee at targeted phases of the gait cycle using a novel, custom-designed set of cable-driven actuators while SCI subjects walk on a treadmill. Partial body-weight support will be provided to ensure a stable stepping pattern on the treadmill with its speed set at maximum comfortable speed. The investigator expects leg-muscle activity will be improved using adaptive resistance training.

Fellowships

Intraspinal Plasticity Contributing to Autonomic Dysreflexia

Hanad Duale, PhD
University of Kentucky
Lexington, Ky.
$98,820 (2 Years)

According to the University of Alabama National Spinal Cord Injury Statistical Center, more than 250,000 people with SCI live in the U.S., with approximately 11,000 new injuries each year. A recent survey assessing the quality of life measures in the SCI population has highlighted that restoring bladder/bowel function and eliminating autonomic dysreflexia (AD) are the first and second highest priorities above walking.

AD is a potentially life-threatening complication of SCIs that occur above the sixth tho-

At the University of Kentucky in Louisville, Hanad Duale, PhD, (back row, second from right) is trying to target what causes autonomic dysreflexia, a potentially life-threatening complication of SCI.

racic spinal segment (T6). It is present after complete as well as incomplete SCI, with an incidence of 50–90%. AD is characterized by a severe increase in blood pressure and a concomitant reduction in heart rate that is commonly triggered by a full bladder or bowel. To date, the precise spinal mechanisms that elicit autonomic dysreflexia are unknown. Using the versatility of viral vector technology, the researcher is in the process of elucidating these supposed spinal mechanisms.

Antibiotic Prescribing for Veterans with SCI&D and Clinician Perceptions

Charlesnika T. Evans, PhD, MPH
Hines Veterans Affairs Medical Center
Chicago
$49,993 (1 Year)

Antibiotic resistance is an increasing problem worldwide, and antibiotics use—whether appropriate or inappropriate—is a driving force in the development of resistance. Prescription of antibiotics has been described in a number of settings, including outpatient facilities in the general population as well as in nursing homes. However, these data are lacking for people with SCI/D. Research in this population may be even more relevant because individuals with SCI/D have increased antibiotics use for treatment of frequent infections, including urinary tract and pressure ulcer.

This study's goals are to assess antibiotic prescribing trends in veterans with SCI/D over time, identify factors associated with prescribing, and determine reasons for type of antibiotic selection with providers of SCI/D care. The main hypotheses are that (1) the rate of outpatient antibiotics prescribing in veterans with SCI/D will remain stable over time, (2) the proportion of broad-spectrum antibiotics used will increase over time, and (3) providers with greater concern about antibiotics use causing resistance in this population will tend to choose narrower spectrum antibiotics.

As the highest-ranking fellowship applicant this year, Dr. Evans has been awarded the Fritz Krauth Memorial Fellowship for this proposal. Fritz Krauth was a PVA member and donor who left a significant legacy contribution to the foundation upon his death in 2002.

Charlesnika T. Evans, PhD, MPH, of the Hines VA Medical Center in Chicago, received PVA's prestigious Fritz Krauth Memorial Fellowship this year. Antibiotics use by veterans with SCI/D is the subject of her research.

For More Information

If you would like to learn more about these grants or the PVA Research Foundation, contact the author at ElinorT@pva.org or visit www.pva.org. ■