UNIVERSITY OF LOUISVILLE
KENTUCKY SPINAL CORD INJURY RESEARCH CENTER

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Improving Quality Of Life For Spinal Cord Injury Patients

Focus on Science: Understanding how the spinal cord can change its circuitry

Jeffrey C. Petruska, Ph.D.

Until about 20 to 30 years ago, the adult mammalian central nervous system (CNS) was considered to be a relatively static structure that was "hard-wired" after the end of its initial development. This view was not seriously challenged, particularly in the context of traumatic injury or an insult like stroke, until a number of important discoveries brought about a broad re-examination of this framework.

We now know that the adult nervous system is anything but "hard-wired." Neurons (nerve cells) of the brain and spinal cord are capable of significant regeneration (re-growth of *injured* cell components). However, in most cases, the brain and spinal cord neurons are either actively prevented from growing, or are not aware they should regenerate.

The presence of signals in the CNS that prevent regeneration are important for maintaining the proper connections between neurons once they are established during development because they prevent "stray connections" from being made. However, they are a significant barrier (literally and figuratively) to the regenerative growth that is required to restore function after insult or injury.

In addition, CNS neurons are often not even "aware" of injuries to their dendrites (the "antennae" of the neurons that receive information from other neurons) or axons (the wire-like portion of the neuron that sends information out to other neurons) for reasons that are not understood. If the neurons don't "know" they have been injured, they would also not "know" to start a growth process that could restore the connections necessary for CNS activities. Thus, at least two issues at play are (1) the need to make neurons "aware" of an injury, and (2) the need to overcome or neutralize the barriers to regenerative growth.

Many researchers try to enhance the regenerative capacity of the CNS neurons by making them more "aware" of injuries and also by enabling them to "ignore" or overcome the barriers to growth. In addition, work is being done to understand and manipulate a growth process that is much more successful than regeneration, and occurs in both the normal and post-injury conditions.

Collateral sprouting (growth of new cell components by *non-injured* neurons) is a process that occurs in many places in both the central and peripheral nervous system (PNS). In contrast to regeneration, neurons undergoing collateral sprouting are *not injured*, and are able to extend new axon branches through the inhibitory environment of both the normal and post-injury spinal cord and brain.

For example, collateral sprouting is part of the changes that underlie the improved abilities of individuals who have received physical therapy after spinal cord injury or stroke. Enhancing the capacity of CNS neurons to undergo collateral sprouting is another approach to improving recovery post-injury. It is expected that sprouting would establish new connections that could enable recovery of functions lost due to injury or insult.

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NeuroRecovery/Network Summit

The Christopher & Dana Reeve Foundation NeuroRecovery Network (NRN) held its 2009 National Summit from Jan. 21-25 in Louisville. Team members from the network's seven clinical centers and two community fitness centers came to Frazier Rehab for five days of advanced training and meetings.

The NRN is a cooperative network of leading-edge rehabilitation centers and community fitness facilities designed to provide activity-based therapies and interventions for promoting functional recovery and improving the overall health of people living with paralysis. Funded by the Centers for Disease Control through a cooperative agreement with the Christopher & Dana Reeve Foundation, the NRN translates the latest scientific advances into effective rehabilitation treatments and is led by Susan Harkema, Ph.D., an associate professor in the Department of Neurological Surgery at UofL.

For the past three years, the National Summit was focused on training new team members, but as the network has matured, the focus has evolved to more advanced topics such as patient progression, case

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Director's Column

Christopher B. Shields, M.D.

KSCIRC clinical trials in spinal cord injury

The clinical component of the KSCIRC is involved in two new clinical trials in spinal cord injury (SCI) that grew out of translational research which originated in the research laboratory. This "bench to bedside" aspect highlights one of the KSCIRC's key strengths: our ability to transfer new innovations developed in our laboratories to patient care in a timely manner. Considering our other strengths in basic science, rehabilitation and clinical treatment, we have a unique ability to participate in these and other clinical trials.

Innovative treatments are being developed at the University of Louisville in conjunction with Norton Healthcare and Frazier Rehabilitation Hospital. The Department of Neurosurgery is one of six participants in the North American Clinical Trials Research Network (NACTN), supported by the Christopher and Dana Reeve Foundation and the Department of Defense.

NACTN has amassed an impressive database on patients suffering acute SCI with follow-up for more than two years on the majority of patients. The first drug to be used in a NACTN-sponsored clinical trial is Riluzole. That trial will begin within the next two months. Riluzole is a sodium channel blocking agent that experimentally has been shown to improve the outcome of SCI in rats.

This work has been repeated in one laboratory and appears to be effective in decreasing the damaging effect of an acute SCI. The first part of this study includes a safety trial of 36 patients (Phase I) followed by a trial of several hundred patients with SCI to determine the effectiveness of Riluzole (Phase II). It is anticipated that results of this study will be available within two to three years.

Another innovative study that will soon begin at the University of Louisville will examine the role of dorsal column stimulation (DCS) of the spinal cord below the level of injury. DCS is a standard method to treat intractable pain of the low back and legs following conditions such as failed back surgery and arachnoiditis. By placement of electrical stimulation over the spinal cord, pain can be decreased.

The rationale for examining the role of DCS in SCI are based on novel experiments performed by Dr. Reggie Edgerton from the University of California Los Angeles, as well as by the engineering department at the California Institute of Technology who are collaborators with us on this study. Dr. Edgerton believes that by utilizing coordinated electrical impulses entering the spinal cord, the central pattern generator (or CPG, a group of interconnected neurons in the spinal cord that control walking) will be stimulated to create effective expression of coordinated muscular activity to the muscles of the legs. DCS will be utilized in conjunction with locomotor training of patients with SCI. The locomotor testing will be performed by Dr. Susan J. Harkema, also a member of the Department of Neurological Surgery at the University of Louisville.

Consent has been obtained from the University of Louisville Human Studies Committee to treat five patients with DCS over the next two years, and these studies will be performed at Norton Hospital and Frazier Rehabilitation Hospital. By combining the effects of DCS and locomotor testing, we predict that patients will improve their ability to stand, walk and maintain coordinated movement of the legs following SCI. By using this innovative electrical stimulation method, we hope to provide an additional way to treat patients with SCI.

It is the expectation that methods being developed and performed by physicians and research scientists at Norton Healthcare, the University of Louisville and Frazier Rehabilitation Hospital will eventually be widely used to increase the ability of patients to regain gait function following paralysis from SCI.

NeuroRecovery/Network Summit

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studies, standardization and advanced locomotor training techniques.

In locomotor training, the body of a paralyzed individual is suspended in a harness over a treadmill, while specially trained therapists or technicians assist the legs in stepping. As the patient improves, he or she needs less help to step and can move from the treadmill to walking overground.

Locomotor training is the first therapy/intervention provided by the NRN, which will expand to other treatment options as new therapies make the transition from the laboratory, through clinical tests, and finally to the public through the NRN.

A second intervention, functional electrical stimulation (FES) is being offered at the two community fitness facilities in addition to locomotor training. FES uses electrical current to stimulate nerves to evoke muscle contractions. It creates patterned movement of the arms or legs, enabling muscles to work and perform active cycling even though the individual may have lost voluntary control of those muscles.

More than 90 people attended the summit from the nine NRN centers and facilities, which are located in Louisville, Philadelphia, Houston, Atlanta, Boston, Los Angeles, West Orange, N.J., and Columbus, Ohio. In addition, more than 20 individuals with spinal cord injuries from the local area graciously volunteered to help team members improve their locomotor training and assessment skills.

The main setting for the summit was the new Spinal Cord Medicine Outpatient Gym on the 11th floor of Frazier Rehab, the home of the lead NRN center. It is equipped with two body weight support treadmills for locomotor training, as well as other standard gym equipment and state-of-the-art audio/visual equipment for reviewing videos and presentations.

In The Spotlight

Jeffrey C. Petruska, Ph.D.

Dr. Petruska, the newest member of the KSCIRC, is the oldest of five children and has lived all over the United States. He was born an "Army brat," but his family moved often even after his father left the service. Dr. Petruska earned a bachelor's degree in psychology from Boston College, where he was also a scholarship athlete, and his Ph.D. in neuroscience from the University of Florida in the laboratory of Dr. Richard Johnson. His recent move to UofL took him from Long Island, N.Y., where he completed post-doctoral training with Dr. Lorne Mendell, former president of the Society for Neuroscience. Through the Mendell lab, Dr. Petruska was an associate of the Christopher and Dana Reeve Foundation's International Consortium on Spinal Cord Injury Research.

His laboratory investigates various forms of axonal plasticity in the normal, injured and treated spinal cord and peripheral nervous system. They are currently examining the effects of post-spinal cord injury physical therapy on spinal motor neurons and circuitry; how noxious/painful stimuli can interfere with physical therapy and other treatments; and whether gene therapy might facilitate or enhance interventions and treatments.

He and his wife, Sara — co-director of the Residency Program in Obstetrics, Gynecology and Women's Health — spend their free time keeping up with their two young children. The entire family is happily integrating with their church and neighborhood communities.

Faculty Honors

Christopher B. Shields, M.D., and Y. Ping Zhang, M.D., were honored at the 2008 Fall Celebration of Faculty Excellence ceremony for their contributions to the university by way of a license for the Louisville Injury System Aparatus (LISA), which assists them in their ongoing endeavors for spinal cord and head injury research. Dr. Shields was unable to attend the Sept. 16 ceremony, but Dr. Zhang was present to accept the certificate. Pictured at the event are (left to right), James R. Zanewicz, director of UofL's Office of Technology Transfer; University President James R. Ramsey, Ph.D.; Dr. Zhang, University Provost Shirley Willihnganz, Ph.D.; and David Wiegman, Ph.D., associate vice president for health affairs/academic affairs in the School of Medicine.

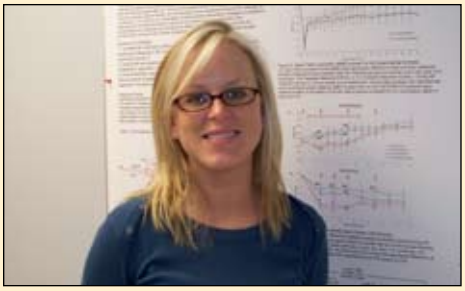
Qilin Cao, M.D., was presented a UofL chair in appreciation of his contribution to the KSCIRC. Dr. Cao has taken a position as an associate professor in the Department of Neurosurgery at the University of Texas at Houston. Pictured with Dr. Cao are KSCIRC faculty (left to right) David Magnuson, Ph.D.; Scott Whittemore, Ph.D.; Jeff Petruska, Ph.D.; Richard Benton, Ph.D.; and Theo Hagg, M.D., Ph.D.

Alexander Ovechkin, M.D., Ph.D., an assistant professor in the Department of Neurological Surgery and the Neuroscience Collaborative Center, received a $150,000 per-year, two-year grant from the Paralyzed Veterans of America Foundation for a research project titled "Respiratory muscle training after spinal cord injury."

Graduate Student Honors

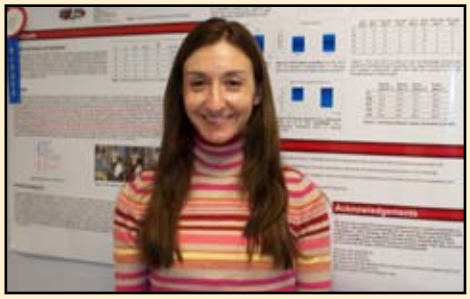
Two trainees from the KSCIRC won top awards at the recent Research Louisville event. They are:

Krista Caudle



First Place: **Krista Caudle**, Department of Anatomical Sciences and Neurobiology — "Wheelchair Restricted Rats and Functional Recovery Following Contusive Spinal Cord Injury." Mentor: David Magnuson, Ph.D., Neurological Surgery. Krista won $500 and travel money to a national meeting of her choice.

Daniela Terson de Paleville



Third Place (tie): **Daniela Terson de Paleville**, Departments of Physiology and Biophysics — "Effects of Locomotor Training on Pulmonary Function in Individuals with Spinal Cord Injury." Mentor: Susan Harkema, Ph.D., Neurological Surgery. Daniela won $100.

Grant Award

Ben Harrison, Ph.D.

Ben Harrison, Ph.D., received a postdoctoral fellowship grant in the sum of $100,000 per year for two years from the Paralyzed Veterans of America Research Foundation. Official title: "Molecular Characterization of *in vivo* Collateral Sprouting." Translation: To determine the genes and proteins responsible for collateral sprouting, an axonal growth process.

Philanthropy News

Day at the Downs

Friends for Michael, a local organization dedicated to advancements in spinal cord injury research and treatment, held its annual Day at the Downs Fundraiser in November.

Pictured (left to right) are FFM supporters Bethany Adams, Jill Farmer and Michelle Bezeley. Farmer is the manager of Therapeutic Recreation & Adapted Sport Programs at Frazier Rehab and Neuroscience Center, and also is president of the Kentucky Wheelchair Athletics.

Michael Feger and his parents, Betty and Mike Perry, enjoyed the day's events.

In the Winner's Circle

One of the day's highlights was a FFM-sponsored race at Churchill Downs. Pictured in the Winner's Circle were owner Ann Lorenson Lynch (fourth from the left) and her husband, accompanied by winning jockey Juilo Garcia. Check out FFM web site at www.friendsformichael.org for more information on the day and upcoming events.

Friends For Michael Inc. also facilitated a daylong “Make A Difference” event to raise money for an all-accessible playground at the new Henry Country Recreation and Services Park on Oct. 20.

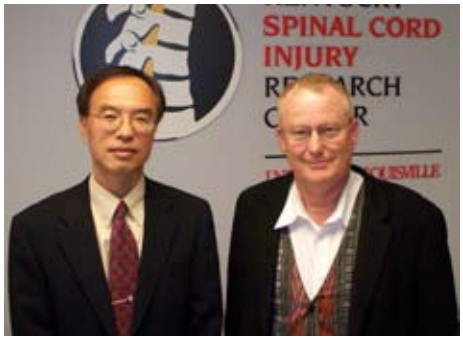
The event featured dinner at the Smith Berry Vineyard and Winery in New Castle, Ky., with entertainment provided by one of Nashville’s newest upcoming country music stars, Michelle Murray (shown at left with Linda and Phil Berry).

Visiting Speakers • Fall 2008

Dr. Theo Hagg hosted Patrick Sullivan, Ph.D., associate director, SCoBIRC; associate professor, Spinal Cord & Brain Injury Research Center and Anatomy & Neurobiology, University of Kentucky.

Dr. Magnuson with Lynne Weaver, D.V.M., Ph.D., Robarts Research Institute, Spinal Cord Injury Lab BioTherapeutics, London, Ontario, Canada.

Dr. Shields with Michael Tymianski, M.D., professor, Department of Surgery, University of Toronto; director, Neurovascular Therapeutics Program, University Health Network, Toronto.



Dr. Whittemore hosted Sheng-Kwei (Victor) Song, Ph.D., associate professor of radiology, Mallinckrodt Institute of Radiology, Washington University School of Medicine.

Dr. Whittemore hosted Marion Murray, Ph.D., professor of neurobiology and anatomy, Drexel University College of Medicine.

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Kentucky Spinal Cord Injury Research Center
University of Louisville
511 S. Floyd St.
Louisville, KY 40292

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The Kentucky Spinal Cord Injury Research Center

Focus on Science

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However, it is becoming clear that collateral sprouting is also responsible for some of the negative outcomes after injuries, such as pain or autonomic dysreflexia (a dangerous condition in which functions like blood pressure and heart-rate become improperly controlled). It is vital that we learn not just about the process of collateral sprouting itself, but also that we learn to separate the mechanisms of axonal sprouting that lead to adaptive/restorative or pathologic/detrimental conditions.

These and other issues are being addressed in laboratories around the world, including some here in the KSCIRC. My laboratory examines some of the ways in which the adult nervous system is able to adapt and change, particularly in terms of changing the connections between neurons. We examine how individual neurons change their chemical and electrical properties, change the structure of their axons, and change the connections they make with other neurons, particularly through collateral sprouting. Understanding the mechanisms and characteristics of collateral sprouting could lead to therapies to harness its potential to enhance recovery after injury through enhancing how *spared* axons and circuitry work, and to prevent the negative outcomes.

Yes, I want to help support research and education at the Kentucky Spinal Cord Injury Research Center so that we can find new treatments for these devastating injuries.

Enclosed please find my tax-deductible contribution of $_____ OR

I pledge a contribution of $_____ to KSCIRC over _____ years.

❑ Yes, please send me regular reminders.

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If you would like to designate how your contribution will be allocated, please express your wishes below. If you do not specify an allocation, the funds will be used where there is the most need.

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