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: Microvascular plasticity as a therapeutic target in spinal cord injury

Richard L. Benton, Ph.D.

Spinal cord tissue, especially the neuron-rich gray matter, is abundantly vascularized due to high metabolic demand. Spinal cord injury (SCI) results in immediate damage to this delicate vascular network, instantly giving rise to bleeding and loss of vascular support. Interestingly, in the days to weeks following SCI, spared blood vessels continue to be pathologically transformed in and around the injury site, exhibiting altered structure and function. Therapies targeting both early as well as evolving vascular dysfunction may hold promise to improve function after SCI. As a first step toward these ultimate therapeutic goals, a better understanding of the precise time course response of spinal vascular responses to injury as well as the molecular effectors responsible for their initiation is critical. Both of these areas are the focus of ongoing collaborative research being conducted in my laboratory and those of Dr. Hagg and Dr. Whittemore.

In the brain and spinal cord, the precise regulation of the microcirculation are provided for by a functional and anatomical network of cells and molecules referred to collectively as the neurovascular unit (NVU). In health, the NVU is primarily composed of endothelial cells (ECs), the principal cell type of blood vessels, which are in turn intimately invested and functionally supported by pericytes and astrocytes. In the normal spinal cord, these cells form a functional network that maintains a robust barrier between the spinal cord and both the immune and circulatory systems, which is referred to as the blood-spinal cord barrier (BSCB). Within hours after traumatic SCI, the BSCB is compromised contributing to the loss of functional nervous tissue.

Until recently, several impediments existed preventing a better understanding of the genes and proteins responsible for this vascular dysfunction. First of all, it has been difficult to determine which aspects of NVU pathology are the results of the physical insult associated with the injury event and which arise via the action of known and unknown molecular regulators. To solve this problem, we have recently developed a novel experimental model of spinal cord vascular injury utilizing a protein produced by ECs called endothelin-1 (ET-1), which is one of the most potent vasoconstrictive compounds known. By applying small amounts of ET-1 to arteries supplying blood flow to the spinal cord, we can induce what is akin to a stroke in the spinal cord. This allows us to very precisely monitor the pathologic activation of the NVU in the absence of overt destruction of blood vessels, which is observed following contusive injury.

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In The Spotlight.

Qilin Cao, M.D., Ph.D.

Dr. Qilin Cao was born in Hunan, a central-south province of China. He earned his M.D. and Master in Medicine from Hunan Medical University (now Central South University Xiang-Ya School of Medicine). While in medical school, he became interested in the neurological diseases and decided to focus his career on academic research. He then worked as a postdoctoral fellow at the University of Freiburg, Germany. Dr. Cao joined Dr. Whittemore's laboratory in the Department of Neurological Surgery, at UofL as a postdoctoral fellow in 1999. He was promoted to assistant professor of Neurological Surgery in 2004. Dr. Cao has witnessed the exciting growth of KSCIRC from two small laboratories to an internationally recognized research center and is extremely honored to be part of it.

Dr. Cao's major scientific interest is in the development of therapeutic strategies to repair the lost myelin, an important insulation around the nerve, after SCI and other neurological diseases such as multiple sclerosis. His laboratory is also interested in identifying the neuroprotective strategies to decrease secondary injury, which is the major contributor for the dysfunction after SCI. Dr. Cao's research is supported by the NIH and the Kentucky Spinal Cord and Head Injury Research Trust. His major research accomplishments thus far has been the demonstration that the combination of transplantation of neural stem cells genetically modified to express growth factors successfully reforms myelin and results in increased

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Director's Column

University of Louisville-Frazier Rehab Institute: A winning partnership

Susan J. Harkema, Ph.D.

As Rehabilitation Research Director of KSCIRC, my mission is to implement a translational research and clinical program to support individuals with spinal cord injury. Essential to our success is the partnership between the University of Louisville and Frazier Rehab Institute. We have established a collaboration among administrators, researchers, physicians, post-doctoral fellows, residents, graduate and undergraduate students, and therapists from the areas of physiology, neurophysiology, exercise physiology, engineering, biomechanics, statistics, physiatry, nursing, physical therapy, occupational therapy. We now have over 30 team members who work together on research projects and clinical integration of therapeutic interventions aimed at recovery of function, health and quality of life after spinal cord injury.

We currently have eight ongoing research studies in humans that focus on retraining the nervous system to facilitate the recovery of standing and walking in individuals with spinal cord injury. Our studies investigate not only physiological characteristics but also secondary issues including clonus, muscle atrophy, bone loss, decreased cardiovascular function, and respiratory muscle weakness. The research is conducted in Frazier Rehab Institute's state-of-the-art facility that has a 2,400 square foot laboratory equipped with four piezoelectric force platforms, specialized in-sole pressure sensor systems and a 10-camera infra-red high-speed motion capture system for understanding the forces and positioning of the body during standing and walking. We have customized electromyographic equipment that measures the activity of the nervous system during many tasks including voluntary movement, standing and stepping. We have four patented Theriastride systems that provide body weight support that is precisely regulated to the individual's level of ability during stepping. They are distributed throughout Frazier Rehab and Neuroscience Center for both research use and clinical application of activity based rehabilitation.

We also monitor breathing and cardiovascular function and scan for changes in muscle and bone. We have four patented Therastride systems that provide body weight support that is precisely regulated to the individual's level of ability during stepping.

Frazier Rehab clinicians and technicians work both in patient care and in research, which gives us access to a very talented group of people who are experts in rehabilitation care. For example, a physical therapist or activity-based technician may provide care in the Frazier Rehab outpatient department in the morning, and then assist with one of our research projects in the afternoon. The research team is an integrated part of Frazier Rehab Institute's Spinal Cord Medicine Program. We have weekly educational seminars to discuss the clinical application of the most current scientific knowledge regarding recovery after spinal cord injury.

One direct example of clinical integration of new research findings is the ongoing cooperative agreement between the Christopher and Dana Reeve Foundation and the Centers for Disease Control and Prevention with the University of Louisville. This program is designed to translate basic science and applied research into intensive activity-based rehabilitation treatment by establishing the NeuroRecovery Network (NRN) comprised of specialized Centers at seven nationally ranked rehabilitation hospitals around the United States. The lead Center for the NRN is located at Frazier Rehab Institute. As director of the NRN, I am tremendously excited that we have enrolled over 220 patients who have been treated with Locomotor Training.

Whether it's by sharing skilled personnel, availability of state-of-the art facilities and equipment, or direct collaboration on research questions, the partnership between Frazier Rehab Institute and the University of Louisville is an invaluable part of our research and essential for our success of providing ongoing continuum of care and cure for people with spinal cord injury.

Pictured are Dr. Harkema's integrated team of researchers that work together to translate the scientific findings to the patients in the clinic.

ABOVE: The research team: Barry McKay, Daniela Terson de Paleville, Sevda Aslan, Janet Quirey, Alexander Ovechkin, Marie-Pascale Cote, Matthew Nitzken, Ashley Carter, David Beneigh, Susan Harkema, Claudia Angeli, Matthew Smith, Christie Ferreira, Yangsheng Chen. (Not shown, Douglas Stevens, Menka Sanghvi and Rebecca Smith)

BELOW: The clinical team - Kevin Johnson, Crystal Simpson, Teri Dugan, Kathy Paper, Kevin Richardson, Dario Klasic, Bryan Maddox, Anthony Gallahar, Jason Hardesty, Lee Smith, Jamie Ochsner, Erica Meadows, Briana Dockins, Djuan Means, Gregory Weathers, Matthew Green, Sara Jerousek, Carrie Zuzick, Cassidy Raibert, Doug McCoy, Brittnay Nathanson, Renee Beck, Mitch Miller, Kyle Carden, Rebekah Morton, Angel Santiago (Not in photo)

In The Spotlight:(contd.)

recovery of locomotor function after SCI.

While not in the laboratory, Dr. Cao enjoys hiking, playing table tennis and most of all, he enjoys swimming in the summer with his wife, Grace and daughters, Rachel, Janna and Victoria. They are active members of their church and loyal supporters of the Louisville Cardinals basketball and football teams.

Note from Dr. Whittemore

It is with mixed feelings that we also must say goodbye to Dr. Cao as he has just accepted a position as an Associate Professor in the Department of Neurosurgery at the University of Texas at Houston. We expect Dr. Cao to be extremely successful there, but will miss his intellectual and scientific contributions, as well as his sense of humor here.

Lee Titsworth's Committee Members

William Lee Titsworth from the Department of Anatomical Sciences and Neurobiology, received his Ph.D.while working on his research at the KSCIRC. Lee is now back in medical school where he will complete his M.D. degree. Pictured here left to right: Xiao-Ming Xu, M.D., Ph.D. (mentor) David S. K. Magnuson, Ph.D., Lee, Theo Hagg, M.D., Ph.D., and Charles Hubscher, Ph.D. (Not shown Matthew Qiu, Ph.D.)

James Massey and Committee

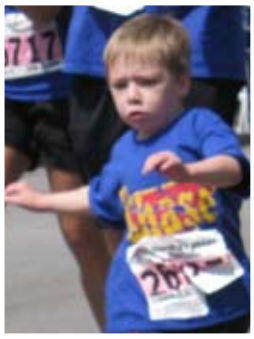
James Massey received his M.D./Ph.D. degrees from the University of Louisville in May. He was in the Department of Anatomical Sciences and Neurobiology while conducting his research at the KSCIRC. Pictured with his committee members, left to right, Fred Roisen, Ph.D., James, Rick Matthews, Ph.D., Stephen Onifer, Ph.D. (Mentor), and Nigel Cooper, Ph.D. (Not shown Xiao-Ming Xu, M.D./ Ph.D.) James is now a resident at the Cleveland Clinic in the field of radiology.

Focus On Science: (contd.)

Another obstacle to therapeutic breakthroughs in this area relates to the relative inability to carefully monitor alterations in EC gene transcription and subsequent protein production caused by SCI. In a recent *Journal of Cerebral Blood Flow and Metabolism* paper, we describe a new technique to purify blood vessels from the injured spinal cord. Using this approach, we have identified several novel genes possibly regulating pathologic NVU plasticity. Not only will these techniques be valuable in the identification of other molecular alterations in spinal ECs, they should also be useful in studying other neurodegenerative disorders with vascular mechanisms, including stroke and multiple sclerosis.

In addition to identification of acute vascular therapeutic targets, we are very interested in identifying specific changes to spinal microvessels arising in the weeks-to-months following the initial injury event. To realize this potential, we look to the successes of our scientific colleagues in the field of cancer biology, where vascular targeting of tumors has led to the development of therapies currently in FDA clinical trials. We recently described changes that arise in spinal blood vessels within the first two weeks following SCI that are identical to observations made in the blood supply in malignant tumors. Ongoing efforts are focused on identifying other vascular targets and testing their value as direct and/or indirect therapeutic targets for the treatment of SCI.

These are just a few examples of how we strive to break through barriers to discovery at KSCIRC. Ultimately, by thinking "outside of the box" and by engaging in productive collaboration, we will achieve our ultimate goal, which is to help those individuals afflicted by SCI and other neurodegenerative disorders to lead healthier, more productive lives.



ABOVE: The first Team Reeve's appearance at the Kentucky Derby Festival's Marathon/ Mini Marathon took place this past April 26. The lead Reeve NeuroRecovery Centers is located at the Frazier Rehab Institute in Louisville. (See Dr. Harkema's Directors column.) This year's efforts were focused on Chase Ford, a five-year old boy who sustained a spinal cord injury at the age of two and was unable to move from the neck down. After working with Dr. Harkema and her group for the past three years, Chase is now able to move his head, arms, upper torso and walk short distances. The Reeve Foundation through a collaboration with the Centers for Disease Control and Prevention, and the University of Louisville's Susan J. Harkema, Ph.D. developed and funded the Locomotor Training that gave Chase back his mobility.

LEFT: Chase and the Team Reeve supporters.

INSET: Chase did some walking in the race and then was pushed by volunteers during the rest of the race.

FFM Auction

The first annual "A Legacy Continues" dinner and auction was held by Friends for Michael on June 5, 2008.

Pictured is Cindy Norton, President of Friends for Michael.

There were many great items at the auction such as this picture of all of the past winners of the Kentucky Derby. FFM Board member (left) Steve Woods and Rickey Timberlake helped make this a successful event.

For upcoming events go to the FFM web site at: http://www.friendsformichael.org

Summer Students

This year there are 11 summer students who are working under several faculty members at the KSCIRC. Hopefully the experiences they gain during the summer will encourage some of them to make the decision to pursue careers in scientific research.

Pictured front row left are: Marcus Siu, Tony Mozer, Chris Carrubba, Allison Siu, Albert Yu,

Back row left: Charlie Westin, Helen Hagg, Allison Liewen, Stuart Bergman, Jonathan Shrader (Not shown, Mark Sansbury.)

The second annual Todd Crawford Foundation run/walk/roll was held in June this year. The event was very successful. Todd hopes that even more people will participate next year.

Todd pictured on the left with some of his friends who ran and rolled the race.

Have wheels will race not matter how big or small.

Dr. Whittemore, Scientific Director of the KSCIRC with Todd after the race. He won't let us tell how long it took.

For upcoming events go to: http://www.toddcrawfordfoundation.org

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The Kentucky Spinal Cord Injury Research Center

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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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