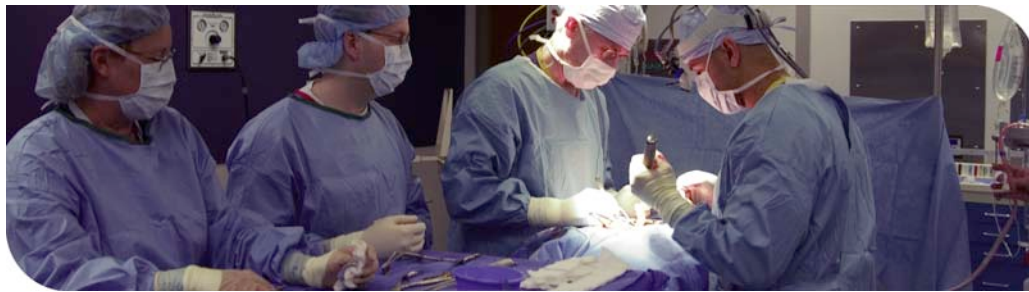


UNIVERSITY of LOUISVILLE
Health Sciences Center



KENTUCKY
SPINAL CORD
INJURY
RESEARCH
CENTER



“Developing successful *spinal cord repair* strategies in the laboratory that can be taken to the clinic in a *timely and responsible* fashion.”

Focus on Science: *Small molecule neuroprotective strategies for SCI*



Theo Hagg, M.D., Ph.D.

Spinal cord injury (SCI) involves both rapid tissue loss due to the initial traumatic insult as well as secondary cell damage that progresses over the first few weeks after the primary injury has occurred. The consensus among researchers and physicians is that if we can rescue even a modest proportion of the spinal cord nerve fibers and tissue by blocking that secondary damage, people with acute SCI could regain a great deal more function.

The Hagg laboratory is developing new experimental neuroprotective treatments that one day might be given to newly injured people via a simple intravenous infusion or a lumbar puncture. Their vision is that such treatments could be started even hours after

the injury, once the diagnosis is made, and that short-term treatments would help the spinal cord get through the first week when most of the second wave of damage occurs.

Currently, there is no FDA-approved treatment that rescues the spinal cord. In many hospitals, new patients receive an infusion of methylprednisolone over the first one or two days. However, this drug cannot be given longer due to its immune-suppressing actions and its benefits are modest at best.

After several years of hard work, the Hagg laboratory has recently made a leap forward by discovering two new drugs that might one day be used in neuroprotective treatments for SCI. In a Kentucky Spinal Cord and Head Injury Research Trust (KSCHIRT)-funded project led by postdoctoral fellow Shojiro Nakashima, in collaboration with Dr. Shields' laboratory, they tested a drug that enhances survival-related signals in cells. After a spinal cord contusion in adult rats, infusion of this drug through a lumbar puncture rescued damaged nerve fibers and their support cells over a 6 week period. Most importantly, the drug greatly improved the sensory and motor functions of these injured animals.

In an NIH-funded project led by postdoctoral fellow Shu Han, and in collaboration with Dr. Whittemore's laboratory, they tested another drug that binds to specific integrin receptors on blood vessels. This drug when given to injured adult mice by daily intra-

venous injections also protected the spinal cord tissue and improved function. They discovered that this drug works by reducing detrimental inflammation in the spinal cord.

As these two new neuroprotective drugs act in different ways they are expected to work even better when combined, something the Hagg laboratory will test soon. In line with their vision to develop clinically relevant treatments, the drugs were as effective when started 4 hours after the injury and had lasting effects weeks after the 1 or 2 week treatments were stopped.

Despite such exciting and promising results, it is always a long road for experimental drugs before they can be approved for use in humans. The next steps will be to determine the ability of these treatments to affect various forms and severity of SCI and to know whether they have side effects in animals.

The collaborative scientific environment created at the KSCIRC promotes synergy and has helped move forward the development of these new experimental treatments. There is a growing understanding among researchers and physicians that the devastating consequences of SCI can be mitigated. However, it will take time, hard work, creative people and major financial support to achieve that goal.

More information about the Hagg lab can be found at <http://www.louisville.edu/kscirc>.

Directors' Column

**Christopher B. Shields,
M.D., F.R.C.S. (C)**

The Kentucky Spinal Cord Injury Research Center (KSCIRC), as a component of the Department of Neurological Surgery, has developed over the past ten years. The genesis of this center was based on the desire to make a meaningful

contribution to finding a cure for paralysis in patients who were afflicted with the tragic outcomes of spinal cord injury (SCI).

After several attempts to accomplish this goal failed during the early years of our department, we were fortunate to have three events converge in the early 1990's to make this dream a reality. They were the generosity of Norton Healthcare in providing seed money to support our research endeavor; the creation of the Kentucky Spinal Cord and Head Injury Research Trust in which all moving traffic violations had a \$12.50 surcharge added to their fine, earmarked for research in spinal cord and head injuries; and the Bucks for Brains program from the state government that was directed through the University of Louisville.

Money obtained from these sources created five endowed chairs in the Department of Neurosurgery, with a sixth added in 2005 following a contribution from Frazier Rehabilitation Institute. Because of this funding, we have been successful in recruiting outstanding research scientists of international reputation.

The clinical department of neurosurgery was founded in 1927 by famed neurosurgeon Dr. Glen Spurling. He created the first neurosurgical program in Kentucky, and founded the American Association of Neurological Surgery and the American Board of Neurological Surgery. He was also the neurosurgeon who treated General George Patton when he suffered quadriplegia following a motor accident soon after the end of WWII. His condition ultimately took his life. Dr. Everett Grantham followed Dr. Spurling, who was succeeded by Dr. Henry D. Garretson.

Dr. Garretson served as chairman of the Department of Neurological Surgery from 1972-1998. Upon my joining the department in 1974, Dr. Garretson and I were the only two neurosurgeons. Since that time, the Department has expanded to eight neurosurgeons and ten Ph.D. research scientists. The entire department is made up of over 100 members.

Currently, faculty and residents in the Department of Neurosurgery at the University of Louisville cover the University of Louisville Hospital as well as a busy private practice at Norton and Kosair

Children's Hospitals. Ours is the only group in Kentucky that covers all subspecialty areas of neurosurgery. In addition, we constitute half (along with the orthopedic spine service) of the Leatherman Spine Center at Norton Hospital, which treats congenital, traumatic, and degenerative afflictions of the spine and spinal cord. All members of the Leatherman Spine Center are full-time faculty at the University of Louisville.

Members of the clinical department are currently involved with six clinical research trials focused primarily on spinal cord and head injuries. Four of these studies take place at the University of Louisville Hospital and two at Norton Hospital. Funding for these studies comes from the Christopher and Dana Reeve Foundation, Department of Defense, American Brain Injury Consortium (ABIC), and Norton Healthcare. A current research trial involves the placement of spinal cord electrical stimulators near the spinal cord below the injury. Spinal cord stimulation is designed to enhance the effects of locomotor training on standing and walking. This operation will be performed in five patients over the next two years. Information from our research laboratories has altered how we treat spinal cord injuries, particularly in the need for early surgery in patients sustaining these injuries.

In the past, it was my vision to create a Neurosurgical Department with several clinical investigators, specifically recruiting neurosurgeons who were experienced in basic research. However, that attempt had limited success. By recruiting a team of outstanding Ph.D. scientists to the Department, we have created a department with clinical and research expertise. Each unit is distinguished by excellence in their respective areas. In fact, our Department is ranked 7th among Neurosurgical Departments in the United States in receiving NIH funding (2005 figures).

The ultimate goal of our research and clinical team is to make significant contributions to patients with SCI that will allow them to lead a more normal life. These advances may include return of bladder, bowel, and sexual function; return of sensory function; and muscle reanimation. The ultimate cure of paralysis remains our single most important motivation to make a meaningful contribution to the field of SCI research.

Each of KSCIRC's three areas of activity — scientific, clinical and rehabilitation — are led by a director, and the three directors manage as a team. Each issue of our newsletter will feature a message from one of the directors, updating you on his or her area of specialization and on the overall momentum of the Center.

In the Spotlight:



Michael Hetman, M.D., Ph.D.

Dr. Hetman was born in Warsaw, Poland. He received his M.D. at the Medical University of

Warsaw. While in

medical school he became interested in neurobiology of diseases and decided to focus his career on academic research. Consequently, he started Ph.D. studies at the Georg August University of Goettingen, Germany and completed them at the Nencki Institute of Experimental

Biology in Warsaw, Poland. Dr. Hetman's postdoctoral training was at the University of Washington. He joined the KSCIRC in 2002 as an assistant professor and endowed chair in Molecular Signaling. The funding for his position was provided by Norton Healthcare, the Kentucky Spinal Cord and Head Injury Research Trust and the Bucks for Brains program of the Commonwealth of Kentucky.

Dr. Hetman's scientific interests are in the development of neuroprotective strategies against neurotrauma and neurodegenerative diseases, molecular dissection of the post-traumatic reorganization of the brain and identification of the key molecular mediators that contribute to the development of brain tumors. Currently, research in his laboratory is concentrated on several signaling enzymes and regulators of gene

expression that may be targeted for neuroprotection, enhancement of post-traumatic adaptations and brain cancer eradication. Dr. Hetman's research is supported by the NIH and the Kentucky Spinal Cord and Head Injury Research Trust. His major research accomplishments include the demonstration of diversity of signaling networks that underlie neurotrophin-mediated neuronal survival, and the discovery of regulatory interactions between a signaling enzyme, Glycogen Synthase Kinase 3beta and the major excitatory neurotransmitter in the brain, glutamate.

With his wife, Joanna, son Adam and daughter Zofia, Dr. Hetman bikes, hikes, cooks or reads and has a wonderful time with his family. His favorite authors include Mikhail Bulhakov and Stanislaw Lem.

KSCIRC Faculty Honored at Doctor's Ball



Pictured here left to right Bob Shircliff, President and CEO Jewish Hospital & St. Mary's HealthCare, Scott R. Whittemore, Ph.D., Susan J. Harkema, Ph.D., Christopher B. Shields, M.D., and Margaret and John Mason, event chairs. Drs. Whittemore, Harkema and Shields, were honored by the Jewish Hospital & St. Mary's Healthcare Foundation for Excellence in Research at the 2007 Doctor's Ball.

Faculty Briefs



It was with great sadness that the KSCIRC bid farewell to our colleague Dr. Xiao-Ming Xu. Dr. Xu was a very important part of building the Center. He has taken a position at Indiana University School of Medicine. However, he will be collaborating with faculty at the Center and as he so aptly put it “it’s only 120 miles away.” He was given a U of L signature chair as a parting gift. Shown here are some of the Center staff at his farewell party.

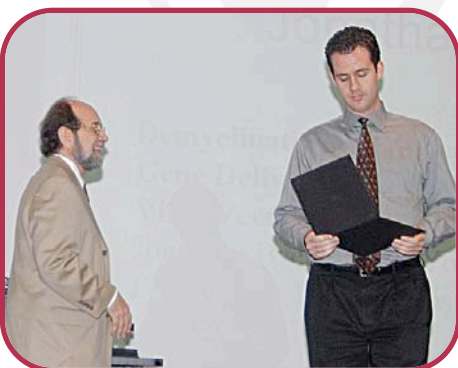
Student and Trainee Achievements



This year’s Research!Louisville student awards included three students who work with KSCIRC researchers. The awards were presented by Dr. Manuel Martinez, Executive Vice President for Research



Second Year Medical Student Toros Dincman won the First Place Norton Healthcare Medical Student Award with his poster titled: “Transcriptomic and proteomic analysis of spinal microvascular endothelial plasticity following focal ischemic spinal cord injury.” His mentors are Scott R. Whittemore, Ph.D. and Richard L. Benton, Ph.D.

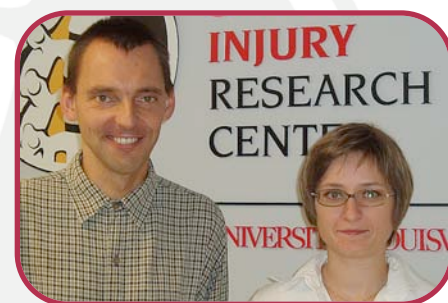


First Year Medical Student Jonathan Byers won with his poster titled: “Demyelination pre-treatment facilitates gene delivery to the spinal cord following viral vector peripheral nerve injection.” His mentor is Christopher B. Shields, M.D.



Postdoctoral Research Fellow Delphine El Mehdi, Ph.D. won first place for her poster titled: “HSP25 expression and phosphorylation induces cellular tolerance and promotes astrocyte process extension after rat spinal cord injury.” Her mentor, Evelyne Gozal, Ph.D. is a member of the COBRE faculty.

Students receiving degrees



Agata Habas with her mentor Michal Hetman, M.D., Ph.D. received her Ph.D.



Jason Beare received his Master of Science degree. His mentor was Scott R. Whittemore, Ph.D.



Jon Kuerzi, with parents Glen and Mary Ann and mentor David S.K. Magnuson, received his Master of Science degree.

Sam Schmidt visits KSCIRC



Sam Schmidt, of the Sam Schmidt Paralysis Foundation visited the KSCIRC in August. He was given a tour, by Drs. Whittemore and Shields pictured here, of the Medical Research Building facilities as well as those in the Frazier Rehab Institute. His foundation assists those individuals with spinal cord injuries including “medical treatment, rehabilitation and technology advances,” as well as funding research endeavors. To learn more go to: <http://www.samschmidt.org>

Guest Speakers



Grand Rounds and Seminars in Neuroscience Speakers

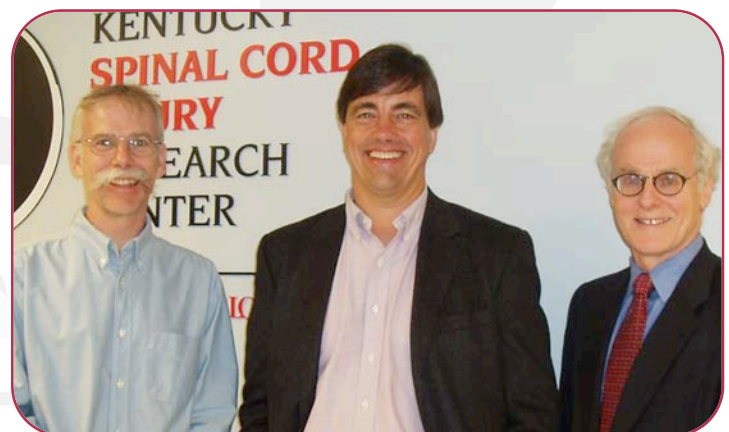
David S. K. Magnuson, Ph.D. and Grand Rounds guest speaker Karim Fouad, Ph.D., Associate Professor of Rehabilitation Medicine, University of Alberta. The title of his lecture was: “Rewiring the injured spinal cord.”



Scott R. Whittemore, Ph.D., hosted Seminars in Neuroscience speaker Gord Fishell, Ph.D., New York University, Smilow Neuroscience Program. The title of his lecture was: “Making up your mind: The developmental origins of cortical interneuron diversity.”



Michal Hetman, M.D., Ph.D. was host to Seminars in Neuroscience speaker Karl Obrietan, Ph.D., Associate Professor, Department of Neuroscience, Ohio State University. The title of his lecture was: “The ERK/MAPK pathway: From circadian timing to seizure-induced cell death.”



Theo Hagg, M.D., Ph.D., Christopher B. Shields, M.D., and Grand Rounds Speaker Christopher Henderson, Ph.D., Professor of Pathology and Cell Biology in Neurology, Co-Director, Center for Motor Neuron Biology and Disease, Columbia University Medical Center. The title of his lecture was: “Mechanisms of motor neuron death in ALS.”

The Kentucky Spinal Cord Injury Research Center



November 19, Friends for Michael Treasurer Stuart Schmidt presented Scott R. Whittemore, Ph.D., Scientific Director of KSCIRC a check for \$15,000. This brings the total given by the group to \$94,000 since 2001. Also pictured are Cindy Norton, President of Friends for Michael, Christopher B. Shields, M.D., Clinical Director of KSCIRC, behind him is Jennifer Hignite VP FFM, Susan J. Harkema, Ph.D., Rehabilitation Director for KSCIRC, Linda Brent Berry, (Michael's mom), Darrell Griffith, former Louisville basketball player and FFM supporter and Denny Crum, former Louisville basketball coach who is also a FFM supporter.

Friends for Michael Day at Churchill Downs is one of their fundraisers. Shown here are pictures of the race they sponsored and some of their members and participants.

FFM is also raising money for a handicap accessible playground in Henry County at the new Community Park. If you would like to learn more about how you can help FFM, go to their web site at www.friendsformichael.org

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