

UNIVERSITY of LOUISVILLE
Health Sciences Center



Focus on Science: *KSCIRC Chosen a Site for the Christopher Reeve Foundation North American Clinical Trials Network*



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

Our mission at KSCIRC is to develop successful spinal cord repair strategies in the laboratory that can be taken to the clinic in a timely and responsible fashion.

A critical component of this process is participation in clinical trials — the process through which new drugs and treatments are tested on a group of volunteers. The most common drugs, diagnostic techniques and procedures in today's medical practice were at one time revolutionary ideas that were tested, proven and improved by the four phases of the clinical trial system.

Dr. Susan Harkema and I are very pleased that KSCIRC will be one of seven clinical investigation sites in the Christopher Reeve

Foundation's (CRF) North American Clinical Trials Network (NACTN). In addition, the University of Texas School of Public Health will be the site responsible for data analysis and management.

CRF believes, as we do, that spinal cord research is at a critical crossroads, where a concerted and coordinated effort needs to be made to move the dozens of therapies that look very promising in the laboratory to human clinical trials so that we can understand how these therapies work across the entire spectrum of spinal cord injury.

One of the key goals of the network investigators, including Dr. Harkema and myself, is to define how we measure variables and progress so that the information we gather from clinical trials will have the broadest application possible. This is very important, because the complex nature of spinal cord injury makes these measurements critical to developing future therapies.

The NACTN will collaborate with a similar network in Europe, with the goal of forming the foundation for a global network.

As more information becomes available, we will keep all of our friends, supporters, patients and colleagues up to date on new opportunities for participation in clinical research through this newsletter and on our web site at <http://www.louisville.edu/kscirc>.

The Clinical Trials Process:

What YOU Need to Know

Every medical breakthrough approved by the National Institutes of Health or the Food and Drug Administration has been through the four phases of the NIH's clinical trials process.

The real heroes of this process are the volunteers. Volunteers, who are properly informed of any risks associated with trial participation, not only help advance science but are also the earliest beneficiaries of the finest medical treatments in the world.

Once researchers test new therapies or procedures in the laboratory and get promising results, they begin planning Phase I clinical trials. New therapies are tested on people only after laboratory and animal studies show promising results.

A Phase I clinical trial is directly built upon basic and animal research and is primarily used to test the safety of a therapy and to estimate possible usefulness in a small number of human subjects.

A Phase II clinical trial usually involves many subjects at several different centers and is used to test safety and efficacy on a broader scale and to determine the best methodology for the bigger Phase III clinical trial to come.

A Phase III clinical trial often involves many centers and sometimes several hundred subjects. The trial usually has two patient groups who receive

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Directors' Column

Welcome to the first issue of our newsletter!

I am **Dr. Scott Whittemore**, the scientific director of the Kentucky Spinal Cord Injury Research Center (KSCIRC). In every issue, either I,

Dr. Christopher Shields, who is our clinical director, or **Dr. Susan Harkema**,

who is rehabilitation research director, will bring you up to date on various aspects of the KSCIRC.

It has been an exciting and challenging eight years since I came to the University of Louisville and the Department of Neurological Surgery. Dr. Shields, Norton Healthcare Professor and Chairman of the Department of Neurological Surgery, had an active but small spinal cord injury (SCI) laboratory, and he recruited me to Louisville to help him achieve his vision of building an internationally recognized SCI research center. It was Dr. Shields' enthusiasm and commitment to this goal that made my decision to move to Louisville very easy. Dr. David Magnuson was also here when I arrived. He was an assistant professor who, along with Dr. Shields, helped me work through the difficult initial years.

When I first arrived, there was no grant funding from the National Institutes of Health (NIH) to support the research of three faculty members. Today, KSCIRC has nine successful principal investigators and has generated grants of more than \$32 million from the NIH, \$9 million from the Commonwealth of Kentucky and \$4 million from private foundations. In fact, last year the Department of Neurological Surgery at the University of Louisville ranked 7th among all neurosurgery departments in the United States in NIH grant support.

The journey to reach these milestones has been an interesting one. Dr. Shields, Dr. Magnuson and I set out an initial five-year plan in 1998 that included attracting at least two senior principal investigators, obtaining a major center grant from the NIH, obtaining new research space and attaining formal recognition from the University of Louisville Board of Trustees as a center. At the time, we based this approach on the fact that we already had one of the strongest neurosurgical groups treating trauma patients in a region extending from Nashville to Indianapolis. Therefore, we initially concentrated on building basic science research.

With the recruitment of Dr. Xiao-Ming Xu from St. Louis University and Dr. Theo Hagg from Dalhousie University, we were able to convince two of the most senior and productive investigators in the field to join KSCIRC. Next, we successfully competed for an \$8.5 million Centers of Biomedical Research Excellence (COBRE)

grant from the NIH and moved into 10,600 square feet of newly renovated research space in the Medical-Dental Research (MDR) Building.

Our next five-year plan included further faculty expansion, renewal of the COBRE grant and building a Rehabilitation Research Program.

Our next recruit was Dr. Michal Hetman, who studies the mechanisms of cell death in neurons. He brought a needed expertise in molecular biology. Dr. Shields recruited neurosurgeon Dr. Todd Vitaz, to the department, and they have developed an NIH-funded research program to assess the severity of SCI immediately after entry to the hospital. (More about this work will be forthcoming in future newsletters.)

Our rationale for developing a SCI rehabilitation program was to quickly and directly affect the quality of lives of our SCI patients. We were very fortunate to be able to recruit Dr. Harkema from UCLA to KSCIRC. Dr. Harkema is well-funded from the NIH and internationally recognized for her work with SCI patients. She, too, will detail her research efforts in this area in a future KSCIRC newsletter. We are presently trying to recruit additional rehabilitation research scientists to build Dr. Harkema's program.

In 2005, we renewed our COBRE grant for an additional five years and \$10.2 million, which will allow our basic research to continue to move forward productively. All of this would not have been possible without the unique partnership between the University of Louisville administration, the Commonwealth of Kentucky and our hospital partners — Norton Healthcare and Frazier Rehabilitation Institute. All have provided considerable resources to enable us to get to where we are and, with their continued support, continue to grow our core programs. It has been incredibly rewarding to see KSCIRC develop into one of the largest and most recognized SCI research centers in the world. We look forward to sharing our future success with you.



Dr. Scott B. Whittemore, University of Louisville President Dr. James Ramsey, and Dr. Christopher B. Shields during the president's recent tour of KSCIRC.

In the Spotlight:



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

Dr. Hagg was born in the Netherlands and raised in South Africa. He returned to Holland where he received his M.D. at the University of Leiden. He later decided that he preferred basic research. Dr. Hagg went on to receive his Ph.D. in Neuroscience from the University of California at San Diego. He has spent the past 22 years studying the biology and function of neurotrophic factors in rodent models with regard to a mixture of neurological disorders that include spinal cord injury. Before coming to Louisville, he lived and worked in San Diego and Halifax, Canada.

Dr. Hagg joined the KSCIRC in 2001 as an endowed chair in Neurological Surgery. His position was funded through Norton Healthcare and the Kentucky Spinal Cord and Head Injury Foundation with support from Kentucky's Research Challenge Trust Fund, or "Bucks for Brains."

His laboratory's research has focused on trying to identify molecules in the nervous system that can be manipulated by pharmacological drugs to protect the spinal cord, enhance new fiber growth and produce new cells. His contributions to this area so far have been in understanding how neurotrophic factors can be used to rescue injured cells in the brain and in the spinal cord, repairing their severed nerve fibers. Research venues over the past decade have also involved studies to understand how stem cells can form new neurons and migrate to different regions of the brain.

Dr. Hagg, his wife, Francine, daughters Else and Helen, and son Koos are avid runners, active in their church, and love a good laugh. They live with a menagerie of animals consisting of two dogs named Rhodie and Ubu, and cat named Hershey. His favorite race to run is the Comrades Ultra Marathon in South Africa. Funny, most of the South Africans come over here to race!

Friends for Michael

Friends for Michael (FFM) is a longtime partner of KSCIRC. A Kentucky-based non-profit 501(c)(3) volunteer organization, FFM raises funds primarily for spinal cord injury research, grants for victims and their families, spinal cord injury prevention/awareness education and scholarships for locally active high school graduates.

For more information, see <http://www.friendsformichael.org> or contact Cindy Norton at **(502) 396-3214**.

Friends for Michael members enjoyed a day at the Kentucky Speedway this summer.



The Kentucky Spinal Cord Injury Research Center

Faculty Briefs

Scott R. Whittemore, Ph.D., gave a lecture titled "Stem cell repair of the injured spinal cord" at the 12th Annual Spinal Cord and Head Injury Research Trust Symposium in Lexington, Ky., on June 6, 2006. In addition, he gave a lecture Aug. 8, 2006 at the University of California Irvine, Reeve Irvine Spinal Cord Center, titled "Stem cell repair of SCI: the vision of KSCIRC." He also has been presenting lectures on stem cell research to various local organizations.

Susan J. Harkema, Ph.D., was invited to give an oral presentation from Aug. 30 to Sept. 2 for "Networks in Motion," the Wenner-Gren Foundations International Symposium, in Stockholm, Sweden, regarding "Recovery of locomotor functions in humans after SCI." Later in September, she was an invited speaker at the Symposium on Advances in Clinical Neurophysiology of Locomotion in Ljubljana, Slovenia, on two different topics: "What we learned from locomotor training about neurocontrol of gait" and "Round table discussion: Clinical protocols for support of recovery of locomotor functions after spinal cord injury."

David Magnuson, Ph.D., presented an invited seminar in June 2006 at Washington University in St. Louis titled "Spinal cord injury: CPG, BBB, LSS, VLF, MMEP, MIER, IHA, HAT." He also presented an invited seminar in September 2006 at Drexel University School of Medicine titled "Re-training the CPG after spinal cord injury."

Richard Benton, Ph.D., traveled to Indianapolis where he gave a lecture to members of the Herman B. Wells Center for Pediatric Research at the Indiana University School of Medicine. The title of his talk was "Vascular mechanisms of secondary spinal cord injury: Therapeutic targets and novel experimental models."

Xiao-Ming Xu, M.D., Ph.D., was an invited speaker at the International Conference on Synapse, Memory, Drug Addiction and Pain that was held in Toronto, Canada in August 2006. At this symposium, Dr. Xu presented the recent work of his lab on spinal cord repair, particularly the combinatorial strategy involving neuroprotection and

axonal regeneration. He also chaired the Brain Disease I Session at the symposium.

Dr. Xu was appointed to the NIH ZRG1 CNNT Study Section as a chartered member from July 1, 2006 to June 30, 2010.

Student & Postdoctoral Research & Awards

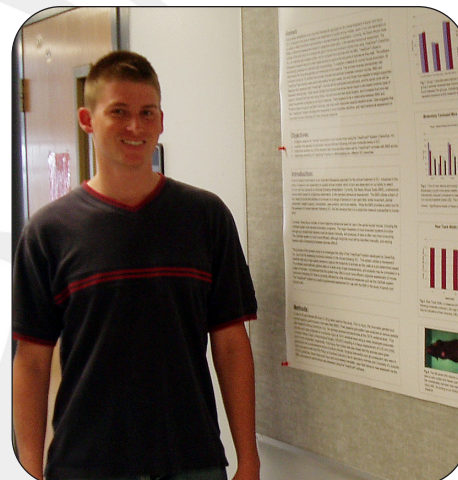


Lee Titsworth, (pictured above) an M.D./Ph.D. student in Dr. Xu's lab, received a four-year NIH F31 fellowship grant starting Aug. 1, 2006. This fellowship, titled "Role of sPLA2 in spinal cord injury and demyelination," was considered outstanding by the Study Section.



Katarzyna Kalita, Ph.D., (pictured above) postdoctoral fellow in Dr. Michal Hetman's lab, won first place for postdocs in *Research!Louisville* for her poster: Role of MKL1 in ERK1/2-Dependent stimulation of SRF-driven transcription in response to BDNF or increased synaptic activity.

Danielle Minnillo, B.A., won 2nd place for year 2-4 medical students at *Research Louisville* for her poster: The effects of cyclooxygenase-2 (COX-2) inhibition on microvascular function and plasticity following experimental spinal cord injury (SCI). Ms. Minnillo then presented her poster at the regional competition for medical students in Omaha, NB (Dr. Whittemore and Dr. Benton - mentors)



Jason Beare, M.S., (pictured above) won 3rd place for graduate students at *Research!Louisville* for his poster: Kinematic analysis of treadmill walking in normal and contused mice using the Treadscan® system. (Dr. Whittemore, Dr. Magnuson - mentors)



Edward Hoyt Brown, MS, (pictured above) defended his masters thesis on November 20, 2006. His thesis was entitled, "The behavioral outcome of swim training at different stages of recovery after incomplete SCI in the rat." (Dr. Magnuson - mentor)

Friends For Michael's Cindy Norton Nominated to National Spinal Cord Injury Association Hall of Fame

Cindy Norton, President of Friends for Michael, was nominated to the National Spinal Cord Injury Association Hall of Fame in the Grassroots Organizer category. This category honors individuals who have demonstrated their ability to energize and mobilize others toward a clear and defined goal associated with improving the opportunities or quality of life for persons living with SCI.

Formed by the National Spinal Cord Injury Association (NSCIA) in 2005, the SCI Hall of Fame was created to recognize excellence and honor individuals and organizations that have made significant contributions to quality of life and advancements toward a better future for all individuals with spinal cord injury.

Bob Kafka, co-director of ADAPT, an accessibility advocacy group based in Austin, Texas, was chosen for the hall of fame in this category in a ceremony at the John F. Kennedy Center for the Performing Arts on October 30, 2006.

"There was an absolutely amazing pool of nominees," said KSCIRC scientific director Scott Whittemore.

"Cindy's inclusion in such an elite group of activists and advocates is real validation for the tremendous work that Friends For Michael does here in Kentucky."

Friends for Michael presented the Kentucky Spinal Cord Injury Center their yearly donation on December 11, 2006. From left to right are: Darrell Griffith, former Louisville basketball player and FFM supporter, Stuart Schmidt FFM Treasurer, Scott R. Whittemore, Ph.D., Scientific Director of the KSCIRC, Cindy Norton, President of FFM, Susan J. Harkema, Ph.D., Rehabilitation Director for KSCIRC, Linda Brent Berry, (Michael's mom), Denny Crum, former Louisville Basketball coach, and Jennifer Hignite, FFM Board Member. Absent from the picture was Dr. Chris Shields, KSCIRC Clinical Director.



The Clinical Trials Process: What YOU Need to Know continued

different treatments, but all other standard care is the same. Many Phase III trials are called double-blind, randomized clinical trials. Double-blind

means that neither the subjects nor the doctors treating the subjects and determining the response to the therapy know which treatment a subject receives. Randomization refers to the placing of subjects into one of the treatment groups in a way that can't be predicted by the patients or investigators.

Most treatments for general use evolve from Phase III clinical trials. After one or more Phase III trials are finished, and if the results are positive for the treatment, the investigators can petition the FDA for government approval to use the drug or procedure to treat patients.

Making a Difference: Philanthropy and KSCIRC

KSCIRC is grateful for the support we receive from all of our donors. This section of our newsletter highlights recent activities and for or to Univ (502)

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Rodney L.
Dr. John M
Gormley
Jessica Mc

2006 Guest Speakers

Dr. Robert Grossman, M.D.

Director, The Neurological



Edgar Garcia-Rill, Ph.D.

Director, Center for Translational Neuroscience, Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, gave a Neurological and Neurology Grand Rounds lecture, January 23 titled "Palliative strategies for spinal cord injury."



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