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UNIVERSITY of LOUISVILLE
Health Sciences Center

KENTUCKY SPINAL CORD INJURY RESEARCH CENTER

Focus on Science: Tackling the Tough Questions in SCI Rehabilitation with Parallel Clinical and Basic Science Research

David Magnuson, Ph.D.

Many aspects of the exciting recent progress in rehabilitation for spinal cord injuries comes directly from basic science research that was accomplished over the past several decades. These new techniques include the body weight supported treadmill training system (BWST) being used by Susan Harkema's laboratory at the Frazier Rehab Institute.

In some ways, however, the rapid progress made in the clinical arena has leap-frogged the work going on in basic science laboratories. This is primarily because there are so few good animal models available that mimic the most commonly seen traumatic SCI in humans.

Marie-Pascale Côté, a post-doctoral researcher in Dr. Harkema's laboratory and Krista Caudle, a graduate student in my laboratory, are creating a collaborative project in which we will be addressing important scientific questions in parallel experiments going on simultaneously in the human and animal laboratories.

A common observation following human SCI is something called 'clonus', which appears as involuntary fast rhythmic activity in ankle muscles that can interfere with the ability to walk or stand. As common as clonus is, it has never been thoroughly described or studied in animal models. Thus, it is very poorly understood and there are currently no proven methods for reducing it without causing undesirable side-effects.

Preliminary data suggest that when SCI individuals undergo multiple locomotor training sessions, clonus and spasticity are reduced. In addition, Marie-Pascale and Krista have found that clonus can also be observed in animal models of SCI and that it has characteristics that are fairly similar to what they observe on a regular basis in SCI patients.

The Behavioral and Electrophysiological Assessment Core facility at KSCIRC recently obtained a Robomedica™ BWST training system for use with animal models of SCI. This device provides a computer-controlled body weight support system combined with a treadmill and robotic arms that can be used either to assist limb movement during training or to assess limb movements after training.

Developed in the laboratory of Dr. Reggie Edgerton at UCLA, Dr. Harkema's former supervisor and current collaborator, the Robomedica™ is leading-edge technology at its best. This device will be used by Marie-Pascale and Krista for experiments that will give us a much better understanding of the spinal networks responsible for clonus and how step training using a BWST can improve functional recovery without the use of drugs and their unwanted side effects.

This collaboration illustrates one of the major strengths of our Center, which is the opportunity for collaborations that include clinical and basic science research, which may speed the application of new techniques in patients and allows individual trainees to gain experience in both areas, paving the way for more research of this kind in the future.

More information about both labs can be found at http://www.louisville.edu/kscirc/.

Directors' Column

Susan Harkema, Ph.D.

As Rehabilitation Research Director of KSCIRC, my goal is to work with our research and clinical teams to facilitate the development of an internationally-recognized translational research and clinical program that supports patients throughout their continuum of care following spinal cord injury.

This begins with their initial care at University Hospital's Level I Trauma Center and other facilities by the faculty of the Department of Neurological Surgery under the leadership of Dr. Christopher Shields. It continues with inpatient and outpatient rehabilitative services at Frazier Rehab Institute and Neuroscience Center.

A recent program extends this support with a Community-based Fitness and Wellness Program in partnership with Frazier Rehab and the Christopher and Dana Reeve Foundation (CDRF).

Research projects are integrated with these clinical programs throughout all stages of care. The goals of these projects are to facilitate those areas that still present a significant challenge to a full recovery.

We have established the Neuroscience Collaborative Center, a partnership of the University of Louisville and Frazier Rehab Institute, where neurophysiologists, graduate students, post-doctoral fellows, residents, physicians, therapists, engineers, biomechanical specialists, exercise physiologists and statisticians work together on research projects aimed at recovery of function, health and quality of life after spinal cord injury. These include current funded research projects that evaluate the use of activity-based therapies for the recovery of standing and walking as well as cardiovascular and respiratory function, muscle strength, and bone integrity in individuals after injury. In this effort, we have collaborators from other universities within the United States and many countries including Canada, Denmark and Russia who visit and contribute to the ongoing research studies.

I also enjoy my role as the Director of the NeuroRecovery Network grant program, funded by a cooperative agreement between the CDRF and the Centers for Disease Control and Prevention, designed to translate basic science and applied research into intensive activity-based rehabilitation treatments. We have established seven specialized centers around the country that provide standardized care based on current scientific and clinical evidence.

The NeuroRecovery Networks' goals include maximizing the availability and quality of rehabilitative care for patients with spinal cord injuries and other neurological disorders; developing a comprehensive database to track the success of activity-based therapeutic interventions; identifying the optimal locomotor training regimens for specific patient populations; and maintaining an administrative network that can supply logistical, technical, and personnel-based support for rehabilitation programs.

I look forward to providing more detailed information about the progress of these research and clinical programs through this newsletter in the future.

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.

KSCIRC Hosts International SCI Research Symposium

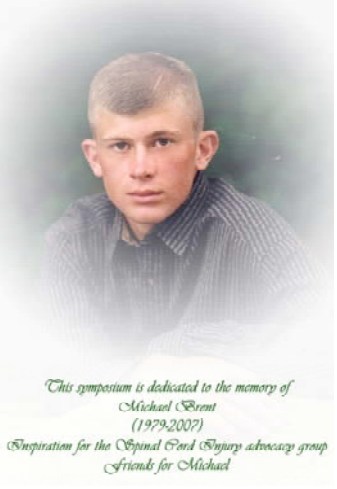
Scott Whittemore, Ph.D.

On June 7th and 8th, the KSCIRC faculty hosted the 13th Annual Kentucky Spinal Cord and Head Injury Research Trust (KSCHIRT) Symposium, sponsored by the KSCHIRT, Norton Healthcare and UofL.

Internationally-recognized scientists from the United States, Canada, Europe, and Australia presented their recent research finding in the areas of Molecular Regulators of Axon Growth, Glial Contributions to CNS Injury, Endoplasmic Reticulum Stress Induced Cell Death in SCI, Epidural Stimulation Following SCI, and Clinical Trials in SCI. The Keynote Address was given by Dr. Sten Grillner of the Nobel Institute in Stockholm, Sweden.

The goal of this symposium was to bring world renowned scientists in very broad disciplines who would not ordinarily get together to discuss research in species as diverse as Drosophila (fruit flies) to man. In this way, KSCIRC investigators and their colleagues at the University of Kentucky's Spinal Cord and Brain Injury Center, many of whom attended the meeting, can develop new ideas for the treatment of SCI and establish new collaborations to move their research programs forward.

The meeting ended with a lively session and discussions on the development and implementation of clinical trials for SCI with some investigators arguing for moving forward quickly and others more judiciously, cautioning for better experimental animal data that had been independently replicated.



There were a record number of 250 attendees who universally lauded the strength of the scientific presentations. The concluding banquet was held at the Muhammad Ali Center with musical entertainment provided by University of Louisville student Patrick H. Hughes. Next year's meeting will be hosted by our UK colleagues June 12-13, 2008 (www.mc.uky.edu/scobirc). The symposium was dedicated to the memory of Michael Brent, inspiration for the Friends for Michael group who passed away April 17, 2007. (www.friendsformichael.org)

Distinguished KSCHIRT Symposium Speakers

Front row left: Alexander G. Rabchevesky, Ph.D., University of Kentucky, M. Douglas Benson, Ph.D., Univ. of Texas Southwestern. Second row: R. Douglas Fields, Ph.D., NICHD, Randal J. Kaufman, Ph.D., University of Michigan, Alan Mackay-Sim, Ph.D., Griffith University Australia, Jan Holsheimer, M.Sc., Ph.D., University of Twente Enchede, The Netherlands, Stuart A. Lipton M.D., Ph.D., University of California San Diego, Keynote Speaker: Sten Grillner, M.D., Nobel Institute for Neurophysiology, Karolinska Institute. Third row: Soren D. Impey, Ph.D., Oregon Health & Science University, Ian Duncan, D.V.M.S., Ph.D., University of Wisconsin, Thomas B. Freeman, M.D., University of South Florida. Back row Larry S. Sherman, Ph.D., Oregon Health and Science University, James L. Salzer, M.D., Ph.D., New York University, Milan R. Dimitrijevic, M.D., Ph.D., Baylor College of Medicine. Unavailable for the picture were: Sha Mi, Ph.D., Giogen Idec Inc, Dietmar Schmucker, Ph.D., Harvard Medical School, Alexei Degterev, Ph.D., Tufts University, V. Reggie Edgerton, Ph.D., University of California Los Angeles, and Wise Young, M.D., Ph.D. Rutgers University.

Dr. Christopher Shields, Dr. Scott Whittemore, Dr. Sten Grillner, (Nobel Institute for Neurophysiology, Karolinska Institute) and Mr. Steve Williams (President and CEO, Norton Healthcare) gather at the KSCHIRT Symposium, sponsored by KSCHIRT, UofL and Norton Healthcare.

Patrick H. Hughes was born without eyes and a condition that does not allow him to extend his arms fully nor walk. Patrick, a student at the University of Louisville, has entertained all over the world and graciously played for the closing dinner of the 13th Annual KSCHIRT Symposium, held at Louisville's Muhammad Ali Center.

In the Spotlight:

Xiao-Ming Xu, M.D., Ph.D.

Dr. Xiao-Ming Xu was born in Ningbo, a city on the east coast of China. He earned his M.D. and Master in Medicine from Shanghai Second Medical University (now Shanghai Jiaotong University School of Medicine). He then came to the U.S. to complete a Ph.D. at the Ohio State University. There, he was mentored by George F. Martin, an internationally-recognized neurobiologist specializing in the development and adaptability of descending spinal pathways. Before coming to Louisville, he completed a postdoctoral fellowship at the Miami Project to Cure Paralysis (University of Miami) and worked at St. Louis University School of Medicine, earning promotion to associate professor.

Dr. Xu joined the KSCIRC in 2001 as the James R. Petersdorf Chair in Spinal Cord and Head Injury Research and was promoted to the rank of Professor in 2005. His position was funded with support from Kentucky's Research Challenge Trust Fund, or "Bucks for Brains" and Norton Healthcare. He has also been a University Scholar since 2001.

His laboratory's research has focused on the development, adaptability and regeneration of the injured spinal cord. His work produced a major breakthrough when he demonstrated that Schwann cells can promote regeneration of axons across a spinal cord lesion gap and, when combined with appropriate factors, can help the axons re-enter the spinal cord.

Another major area of inquiry for Xu is secondary injury mechanisms in SCI. His team has targeted an enzyme named phospholipase A2 as a molecule that affects the biochemical injuries that occur after SCI. They are trying to identify a therapy to block this enzyme and, hopefully, prevent injury at the biomolecular level. He hopes that this research can be transferred to clinical treatments for patients.

Dr. Xu's research is supported by grants from the National Institutes of Health, the International Spinal Research Trust, the Daniel Heumann Fund for Spinal Cord Research, the Paralyzed Veterans of America, the Kentucky Spinal Cord and Head Injury Research Trust Fund, Norton Healthcare, "Bucks for Brains" and the University of Louisville.

Dr. Xu has a close family including his wife, Tao, and his daughter, Lisa. While not working, he enjoys reading, traveling, photography and listening to music. His favorite sports are fishing, Tai-Ji and walking.

Dr. Xu accepted a new position at Indiana University School of Medicine as the Primary Investigator of the Stark Neuroscience Research Institute, Professor of Neurological Surgery, Mari Hulman George Chair in Neuroscience Research and Scientific Director of the Spinal Cord and Brain Injury Research Group. He has mixed feelings about his new job. While it is a great opportunity, he will really miss the people here with whom he has worked closely and the wonderful friendships that have been built. Fortunately, the distance between the two cities is only 120 miles!

SCI Walk Event:

Todd Crawford (Left) and Trey Crawford, founders of the Todd Crawford Foundation, (www.toddcrawfordfoundation.org) enjoy the first annual run, roll, walk June 9. The event raised more than $8000 and "TEAM SPINAL CORD" represented KSCIRC with enthusiasm!

Above: Dr. Theo Hagg (front with cup) at the start of the 5k run, walk, roll event.

Team Spinal Cord members Francine Hagg, Scott Whittemore, Scott Smith & Theo Hagg (behind). Lee and Mary Beth Titsworth, Eddie Brown and Jon Kuerzi also participated.

Faculty Briefs

Christopher Shields, M.D. and **Scott Whittemore, Ph.D.** were honored at Business First's "Partners in Healthcare" annual event.

Theo Hagg, M.D., Ph.D. has published the following journal articles:

- Hagg T., Endogenous regulators of adult CNS neurogenesis. Curr Pharm Des. 2007,13:1829-40.
- Adam Baker K, Nakashima S, Hagg T. Dorsal column sensory axons lack TrkC and are not rescued by local neurotrophin-3 infusions following spinal cord contusion in adult rats. Exp Neurol. 2007, 205:82-91.
- Yang P, Dankowski A, Hagg T. Protein tyrosine phosphatase inhibition reduces degeneration of dopaminergic substantia nigra neurons and projections in 6-OHDA treated adult rats. Eur J Neurosci. 2007, 25:1332-40.
- Baker KA, Hagg T. Developmental and injury-induced expression of alpha1beta1 and alphabeta1 integrins in the rat spinal cord. Brain Res. 2007, 26:1130:54-66.

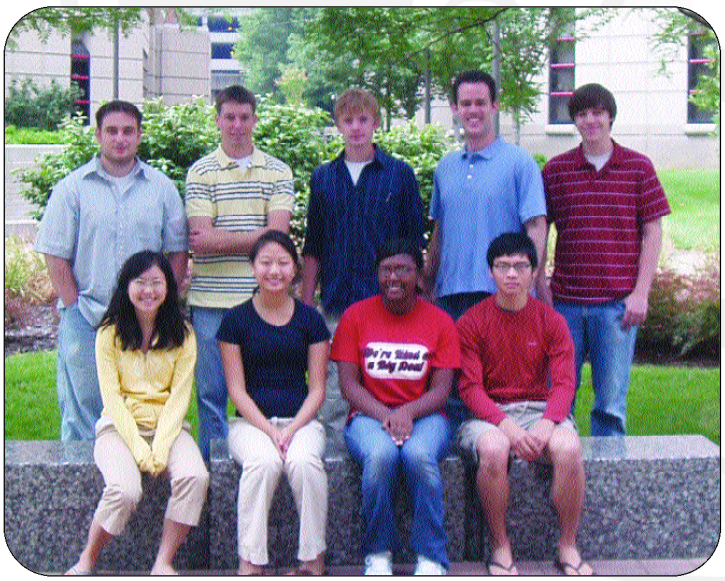
David Magnuson, Ph.D. gave a talk at the University of Alberta in Edmonton, Alberta July 6, 2007. The talk was titled: "Re-training the CPG after spinal cord injury: Swimming and walking."

Scott Whittemore, Ph.D. gave the following lectures:

- April, 2007 at the Center for Translational Neuroscience, Dept. Neurobiology & Developmental Sciences, University of Arkansas Medical School, "Stem cell repair for CNS injury."
- April, 2007 a Keynote Address at the Society for Biomaterials 2007 Annual Meeting - Chicago, "CNS Stem Cell Repair: What the bioengineer needs to know."
- May, 2007 at Neuroprotection and Neurorepair: From Pharmacology to Stem Cells, UMDNJ, Newark, "The Therapeutic Potential of Stem Cell Repair for Spinal Cord Injury."
- July, 2007 at the 3rd Annual Research Symposium on New Frontiers in Spinal Cord Repair, Ohio State University, "The Myths and Realities of Stem Cell Repair for CNS Injury."

Michal Hetman, Ph.D. gave a lecture: "Neuronal response to transcriptional inhibition." International Institute of Molecular and Cell Biology, Warsaw, Poland, June 20, 2007.

KSCIRC Summer Students



Students working in the KSCIRC labs during the summer are: (Front row) Ga-young Joung, Anne Yang, Danielle Cole, Marcus Siu. (Top row) Toros Dincman, Kenny Buckardt, Charlie Westin, Drew Byers and Bennett Rummel**.** Absent are: Allison Siu and Albert Yu.

Students and Post Docs from the KSCIRC who participated in the 2007 Neuroscience Day poster contest won in several categories. They are:

Giorgi Kharebava, Ph.D. (Hetman lab) won second place in the post doc division for his poster titled, "MAPK prosurvival cascade integrates PDK1 signals to protect trophic deprived cortical neurons."

Peng Yang, M.D., Ph.D. (Hagg lab) won first place in the post doc division for his poster titled, "CNTF mediates dopamine D2 receptor-induced neural precursor proliferation in the adult forebrain subventricular zone."

Yongjie (Jacky) Zhang, M.D. (Shields lab) won first prize for graduate students for his poster titled, "The role of CSF blockage and AQP4 expression in posttraumatic syringomyelia."

POST-DOCTORAL GRANT

Rebecca Smith, Ph.D. (Magnuson Lab) received a post-doctoral fellowship grant from the Paralysis Project of America for a collaborative project with Dr. Richard Benton titled, "Vascular function, inflammation and early training after SCI."

Grand Rounds and Seminars in Neuroscience Speakers

Wendy Macklin, Ph.D. with Dr. Qilin Cao

Cleveland Clinic Foundation, Department of Neuroscience gave a Seminars In Neuroscience lecture, February 22, 2007 titled: Signaling controlling oligodendrocyte differentiation."

Marie-Francoise Chesselet, M.D., Ph.D.

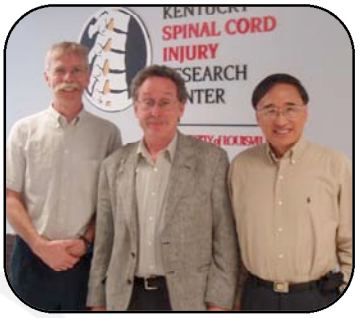
Chair of the Department of Neurobiology in the David Geffen School of Medicine at UCLA. She is also Director of the APDA Advanced Center for Parkinson's Disease Research, Morris K. Udall Center of Excellence for Parkinson's Disease Research and the Center for Gene Environment Studies in Parkinson's Disease at UCLA gave a Seminars in Neuroscience lecture, March 22, 2007 titled: "Parkinson's disease: Novel insights from genetic mouse models."

Phillip Popovich, Ph.D.

Associate Professor, Ray W. Poppleton Research Chair, Director, Center for Brain and Spinal Cord Repair, Department of Molecular Virology, Immunology & Medical Genetics, Department of Neuroscience, The Ohio State University gave a Grand Rounds lecture, April 24, 2007 titled: "Central and peripheral consequences of activating the immune system after spinal cord injury."

Itzhak Fischer, Ph.D. with Drs. Theo Hagg & Xiao-Ming Xu

Professor and Chair, Department of Neurobiology and Anatomy, Drexel University College of Medicine gave a Grand Rounds lecture May 22, 2007 titled: "Transplanting neural stem cells into the spinal cord: Progress report."



Board of Overseers Tour KSCIRC Facilities

Members of the University's Board of Overseers visited the KSCIRC May 15. They were given a tour of the Medical Dental Research facilities by Drs. Whittemore, Shields and Magnuson and by Dr. Harkema at the Frazier Rehab Institute. Members were very impressed with the facilities and scientific work being done.

Recent Event:

June 8th and 9th, 2007.

International Workshop on Epidural Stimulation: The recovery of standing and walking after human SCI. Hosted by KSCIRC and the Department of Neurological Surgery at the University of Louisville. The purpose of the workshop was to discuss the potential of using epidural stimulation to facilitate standing and stepping after spinal cord injury in humans as well as reduce pain and spasticity. The workshop was launched by lectures given by V. Reggie Edgerton, Milan Dimitrijevic and Jan Holsheimer on Friday June 8th as Session IV of the 13th Annual KSHIRT Symposium (pages 2, 3). The workshop continued on Saturday and Sunday June 9th and 10th at the Frazier Rehabilitation Institute. Other noteable participants included Prof. Sten Grillner (Stockholm), Yuri Gerasimenko (St. Petersburg) and Dr. Vivian Mushahwar (Edmonton).

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