



Improving Quality Of Life For Spinal Cord Injury Patients

Focus on Science: DNA damage: A common denominator of age- related neurodegenerative diseases and neurotrauma



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

The neurological deficits displayed by the patients who suffer from traumatic brain or spinal cord injuries are consequences of either direct, immediate damage or indirect, delayed damage of the nervous tissue. While the first one could be compared to a car accident causing a crack in the cooling system leading to a leak, the latter would correspond to the unavoidable engine breakdown that would follow if the affected car is kept running despite the coolant leak. Thus, the immediate effects of the initial mechanical force acting on the nervous system trigger a whole series of events precipitating secondary damage of various cellular components of the nervous system. While neurotrauma prevention is the only way to avoid the immediate damage, it is hoped

that secondary damage can be reduced by appropriate therapies to reduce the neurological deficits in neurotrauma survivors. To rationally develop the effective neuroprotective therapies, we need the knowledge of the mechanisms underlying this secondary injury.

DNA is the macromolecule that stores the genetic information needed for the development of an organism and maintenance of its cells and tissues. Although DNA is a relatively stable compound, it can be damaged by reactive chemicals including oxidants. Repair of such gene damage can result in mutations leading to cancer. Also, DNA damage disrupts the reading and execution of the genetic instructions of cell maintenance in cells, even in cells that can not develop tumors. If DNA damage is severe, it initiates cell death, which in the case of tissues with minimal cell replacement, leads to irreversible cell loss. Of note, the accumulation of naturally occurring oxidative DNA lesions is a likely key factor facilitating the development of age-related neurodegenerative conditions such as Alzheimer's or Parkinson's diseases. In addition, oxidative DNA damage is believed to be an important contributor to the pathology of the secondary damage following stroke or neurotrauma. Thus, intense DNA damage would trigger loss of glial cells and neurons while milder persistent damage would keep them malfunctioning and unresponsive to repair therapies such as plasticity-promoting rehabilitation or regeneration. As neuronal replacement is minimal, neuron death would irreversibly decrease the functional capabilities of the brain or the spinal cord.

To counteract the dire consequences of DNA damage in the nervous system we need to identify the factors that determine

KSCIRC receives \$4.7 million from the NIH

At a news conference held February 18, University of Louisville President Dr. James R. Ramsey recognized three KSCIRC researchers for receiving \$4.7 million in grant money for research in spinal cord injury from the National Institutes of Health and \$300,000 from the Kentucky Spinal Cord and Head Injury Research Trust. Scott R. Whittemore, Ph.D., the Henry D. Garretson Endowed Chair in Neurological Surgery and Scientific Director of the KSCIRC received \$1.9 million, Theo Hagg, M.D., Ph.D., Endowed Chair in Neurosurgery received \$1.5 million, Qilin Cao, M.D., Ph.D., received \$1.6 million.

Dr. Ramsey told reporters that Drs. Whittemore and Hagg were recruited with Bucks for Brains money and feels that this money is "key in investing in people." The KSCIRC group is competing with some of the top research facilities in the country for grant dollars. The KSCIRC is part of the Department of Neurological Surgery at the

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Dr. Ramsey and Dr. Whittemore



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Director's Column



Mentoring Trainees: One of the most important responsibilities of our job.

Scott R. Whittemore, Ph.D.

When the lay and scientific worlds see and recognize the successes of the KSCIRC, that recognition most often goes to the individual faculty members who have made those accomplishments. What usually goes unrecognized are the contributions to that work made by our graduate students and postdoctoral fellows. Often, it is the trainee that does all or the majority of the actual experimental work. I wanted to share with you the importance of our trainees, how their relationships with their Principal Investigators (Mentors) evolves, and how significantly we as a faculty take our responsibility to train this next generation of SCI researchers.

When a graduate student or postdoctoral fellow joins a laboratory, there are expectations on both sides that should be met for the arrangement to benefit both the trainee and the mentor. In the case of graduate students, these are very intelligent and motivated recent college graduates who often have little laboratory experience and little familiarity with the specific area of research in the laboratory. The role of the mentor is to initiate their independent thinking as a scientist and together develop a series of research projects that will form the basis of their doctoral dissertation. My personal expectations are that by the time a graduate student has completed a full year in my laboratory, they will be at the point where they help drive new experimental directions and move their individual projects forward.

In contrast, when a postdoctoral fellow comes into the lab with their Ph.D. and/or M.D. degree in hand, they most often have significant independent laboratory experience gained during their doctoral studies. Our expectations for the level of independent scientific thought of postdocs are significantly higher than

that for incoming graduate students. A postdoctoral fellow functions much as a Resident does in the hospital setting after she/he complete their M.D. training.

In many ways, one's trainees are like your children. You try to give them every opportunity to succeed and expect that their ultimate accomplishments will exceed your own. We have been fortunate at the KSCIRC to have been involved with a large number of very talented graduate students and postdoctoral fellows. Since 1998, we have graduated 6 M.S. and 13 Ph.D. students and trained 17 postdoctoral fellows. All have moved on to successful positions, in academia, medicine, or the biotechnology field.

To highlight but a few of these achievements, Kentucky natives Satish Rao and Alyson Spille received their M.S. degrees in the KSCIRC and went on to complete medical school at UofL. Fellow Kentuckians David Loy and Jason Talbott completed their Ph.D. training in the KSCIRC and received their M.D. degrees from UofL and are now in radiology residency programs at Washington University and University of California San Francisco, respectively. Qilin Cao and Richard Benton started as postdoctoral fellows in the KSCIRC and are now Assistant Professors at UofL in the Departments of Neurological Surgery and Anatomical Sciences & Neurobiology, respectively. Our other graduates have achieved similarly stellar track records of which we, as a faculty, are very proud.

Pictured here are our current graduate students and postdoctoral fellows. They are well on their way to being outstanding independent scientists. We as a faculty would not be successful without their very significant contributions to our research programs and we thank all of them, past and present, for the important roles that they have played in our research successes.

Graduate Students below: Front row (L-R): Rachel Hill, David Beneigh; Back row (L-R): Scott Smith, Sheila Arnold, W. Lee Titsworth, Janelle Fassbender, Krista Caudle (missing: Chunling Fan)



Postdoctoral Fellows below: Front row (L-R): Panpan Yu, XiaoXin Cheng, Marie-Pascale Cote; Back row (L-R): Srikanth Rajagopalan, Giorgi Kharebeva, Shu Han, Sevda Aslan, Rebecca Smith, Denys Makonchuk, Deepti Nair, Sujata Saraswat, Cynthia Gomes, Ian Zheng, Zhen Gu (missing: Aruna Vashishta)



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.

Dr. David S.K. Magnuson, who is still “only” a Canadian, was born in Saskatoon, Saskatchewan and learned to skate before

he could walk. He grew up in Tsawwassen, British Columbia and played hockey for Trinity Western College before moving to the University of Victoria to finish his undergraduate degree. He then headed to the University of British Columbia to get his Ph.D. in Physiology and did postdoctoral work at University College, London and at the University of Ottawa in Ontario. His first faculty position was at the University of Manitoba in the Spinal Cord Research Center headed by Dr. Larry Jordan.

Dr. Magnuson came to UofL in 1995, prior to the formation of KSCIRC. His initial research here began with a strong interest in how the normal spinal cord generates locomotor patterns. His work focused on using the excitotoxin kainic acid to kill spinal cord interneurons in different locations in an effort to determine which populations are critical for pattern

generation. In addition, his laboratory has investigated the long ascending and descending pathways in the spinal cord that are responsible for initiating and modulating locomotion. More recently, his talented laboratory team has been using animal models of rehabilitation to study how the central pattern generating circuitry can be re-trained to produce meaningful activity after an incomplete spinal cord injury.

When not in the laboratory, David is with his family at, or on the baseball field, or in the wilds of Cumberland County where they have a fishing camp. He and his wife, Julie, have had the pleasure of (almost) raising three great kids in Louisville, Trystan (22), Sam (19) and Blythe (14). They are active members of their church and avid supporters of the Louisville Cardinals and Toronto Blue Jays baseball teams.

KSCHIRT Rehabilitation Research Meeting

On November 10, 2007, Dr. Harkema hosted the SCI Summit “Advances in Spinal Cord Injury Treatment”. Over 200 physicians, health care providers, scientists, and people from the SCI community attended this bi-annual meeting. The goal of this meeting was to educate both the scientific and lay communities on recent advances in SCI research and rehabilitation.

The keynote speaker was Michael Fehlings, M.D., Ph.D., Professor of Neurosurgery and Krembil Chair in Neural Repair and Regeneration, University of Toronto. Other distinguished speakers included Jefferson County Senator Tim Shaughnessy, Dr. Susan Harkema, Ph.D., Dr. Christopher Shields, M.D., Christopher Schrepferman, M.D., Douglas Stevens, M.D., Medical Director of the Spinal Cord Medicine Program at Frazier Rehab and Neuroscience Center, and Randy Snow, Fortune 500 speaker.



Dr. Whittemore, Dr. Fehlings, Dr. Harkema, Dr. Shields, and Dr. Stevens

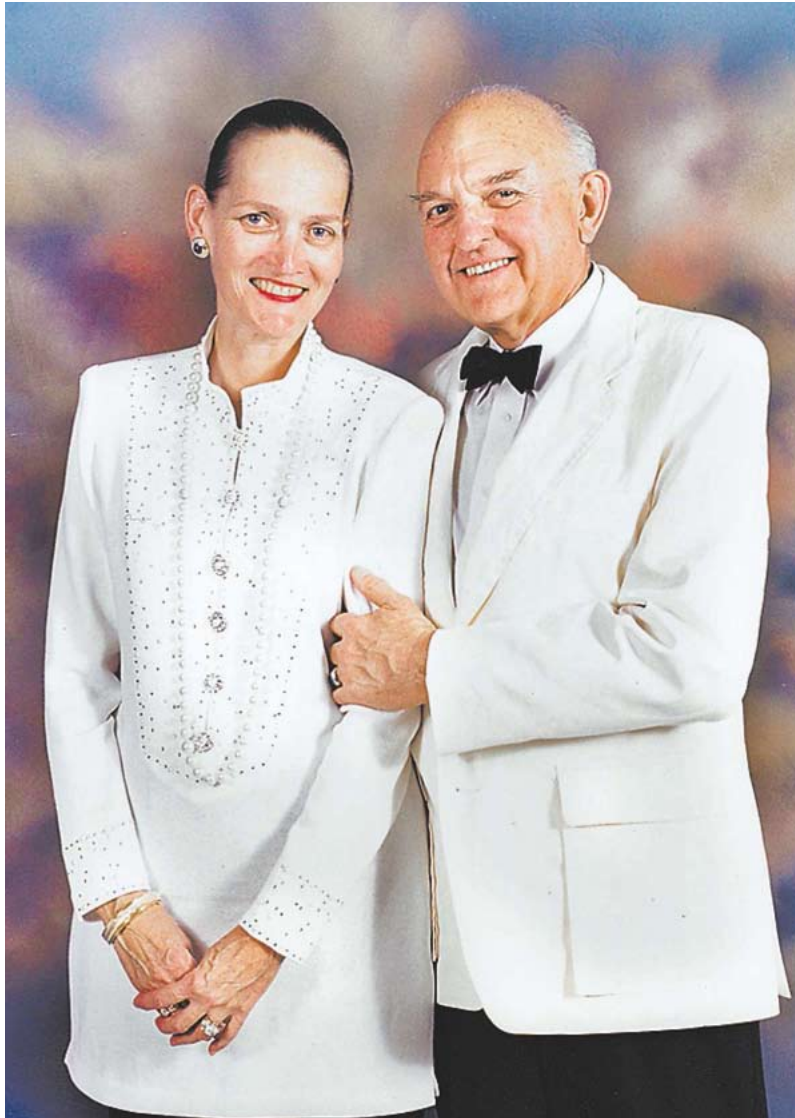
While the lively discussions likely raised more questions than they answered, all of the attendees agreed that the very strong scientific program was beneficial in bringing the Louisville SCI community ‘up to speed’ on current research and rehabilitation advances.

Remembering Dr. and Mrs. Garretson

Henry D. Garretson and his wife Marianna Garretson died on December 8, 2007 when their single engine plane crashed near Bardstown, Kentucky.

Dr. Garretson's contributions to organized neurosurgery were significant, including election as Presidents of the American Association of Neurological Surgeons (1987-1988), the Academy of Neurological Surgeons (1991-1992), the Society of University Neurosurgeons (1983-1984), and the Southern Neurosurgical Society (1986-1987). He was a member of the American Board of Neurological Surgery (1981-1987) and was its Chairman in 1986-1987. He continued to serve as a guest examiner for many years thereafter. Henry and Marianna were both gracious hosts for the many meetings that they hosted.

In addition to holding positions in national organized neurosurgery, Dr. Garretson was instrumental in creating the Department of Neurological Surgery at the University of Louisville in 1994. This department currently includes seven neurosurgical faculty members and a research team of 8 Ph.D.s (6 holding Endowed Chairs). One of the endowed chairs is named the Henry and Marianna Endowed Chair in Spinal Cord Injury. He was a member of the Board of the Kentucky Spinal Cord and Head Injury Research Trust that oversees the distribution of research funds for neurotrauma collected from speeding tickets in Kentucky. Henry was chief of the medical staff at Norton Hospital in



Louisville and was a member of the Board of Directors for several years. He was also Vice-Dean for Clinical Affairs at the University of Louisville School of Medicine.

Henry and Marianna were born in Tucson, AZ, and both graduated from the University of Arizona. Henry graduated from Harvard University Medical School in 1954 and obtained his neurosurgical training at the Montreal Neurological Institute (MNI) under Drs. Wilder Penfield, William Cone, Ted Rasmussen, and William Feindel. He obtained his Ph.D. from McGill University studying the doubling time of the glioblastoma multiforme. Henry remained on faculty at the MNI for 8 years before being recruited to Louisville where he became the first

full-time Chief of the Neurosurgical Section (Surgery), which was founded by Dr. R. Glen Spurling in 1927. While in Louisville, Henry became known for his seminal work on the surgical treatment of large AVMs under local anesthesia. He also developed a large epilepsy practice following techniques acquired in Montreal.

As President of many major neurosurgical organizations, Henry was highly articulate, a shrewd negotiator, and eminently fair in his decisions. He was able to evaluate difficult problems and deal with them in a rational manner that was eminently fair. He remained close friends with many leaders of neurosurgery until his untimely death.

Henry was a flight surgeon for the U.S. Navy for 3 years, having obtained his training in the School of Aviation Medicine in Pensacola, Florida. He started flying his own plane 15 years ago and became

an enthusiastic student of flight. He took meticulous care of his Cessna 150, having it frequently serviced to maintain it in perfect condition. Henry and Marianna's trips were usually between their homes in Louisville and Kiawah Island, South Carolina, but they would frequently take shorter trips for the sheer enjoyment of flying. He was particularly close to those neurosurgeons who also shared an interest in aviation, often comparing notes on additions to their planes.

Henry and Marianna are survived by two sons, John and Steven, and two grandchildren. John, living in New York, is a member of the largest patent law firm in the United States, and Steven is a businessman in Louisville.

Neural Recovery Network (NRN) holds training session at Frazier Rehab Institute.

The NRN is funded by the Christopher and Dana Reeve Foundation. It's mission is to provide support for the development of specialized centers that provide standardized activity-based rehabilitation care based on current scientific and clinical evidence for people with spinal cord injury and other selected neurological disorders. The initial focus of the NRN is on Locomotor Training. The lead Center of the NRN at the University of Louisville and is directed by Susan J. Harkema, PhD, Associate Professor of Neurological Surgery. Dr. Harkema holds the Owsley B. Frazier Rehabilitation Chair and is the Rehabilitation Research Director of the KSCIRC as well as the Director of Research at Frazier Rehab Institute. In January, 2008, the NRN center at Frazier Rehab Institute hosted a five-day intensive training that was led by senior team members for initial training of new



clinicians, and advanced training for those clinicians already involved in the Network. Over 85 clinicians, researchers and therapists from seven rehabilitation sites attended the summit over the five days and participated in the hands-on training in the theory and techniques of Locomotor Training. Dr. Harkema will provide more information on the NRN in one of her upcoming Director's Columns.

Focus on Science: (continued)

the reaction of nerve cells to DNA damage (cell death vs. cell survival with repaired or un-repaired genes) and develop survival/recovery treatments. Also, if we can not restore genomic integrity, could we improve the reading efficiency of the genetic information that still remains intact? My research program is aimed at answering these and other related questions.

The major portion of the genetic information resides in the cell's nucleus. Within the nucleus there is also a smaller sub-compartment called the nucleolus. The nucleolus is a residence for a special class of genes that encode ribosomal RNA (rRNA). These genes are very actively "read" or expressed, accounting for at least a half of all the genetic information "reading" output. Their product, rRNA makes the key component for the ribosomes, which are the cellular protein factories. Intriguingly, we found that the DNA damage that was able to kill neurons by a cell suicide pathway known as apoptosis also blocked the expression of rRNA genes. Indeed, our further studies established that DNA damage induces neuronal apoptosis by selective damage of rRNA genes. An exciting possibility that is implied by these results is that the rRNA genes may be reasonable candidates for the genome repair strategies of neuroprotection.

However, before the genome integrity restoration could come to the rescue, the cells must be kept on a cell "life support." Research performed in my lab indicated that this temporary survival may be achieved by manipulating a cellular enzyme known as MAP-kinase (or ERK1/2) that transmits the information from the cellular environment to the cell response apparatus. We identified the molecular determinants of the neuroprotective MAP-kinase activation and discovered that it can also be activated by pharmacological agents that act on another cellular signaling transducer, the cyclic AMP.

Our studies may result in new therapeutic strategies that would be applicable to conditions ranging from Alzheimer's disease to traumatic spinal cord injury. More information on the DNA damage research at the KSCIRC can be found at www.kscirc.org/hetman/HetmanIndex.htm.



KSCIRC Graduate Students Receive Ph.D.s

Pictured (L-R) Scott R. Whittemore, Ph.D. and his trainee Ahmed Abdellatif, M.D., Ph.D., Agata Habas, Ph.D. and her mentor Michal Hetman, M.D., Ph.D.

KSCIRC receives \$4.7 million from the NIH (continued)

University of Louisville which ranks seventh in the country in funding from NIH. The funding is extremely competitive now with only one out of ten grant submissions being funded. The success of these grant awards are a direct result of the quality of the researchers who have been recruited with the help of the Bucks for Brains money, which was supplied through the State funding source and matched by private donors to the University to endow chair positions which in turn bring in some of the top research scientists in their field of expertise.

The return on the Bucks for Brains money for this group has been outstanding. With an initial \$6 million from the Bucks for Brains money matched by Norton Healthcare (more than \$3.3 million) and Frazier Rehab Institute (more than \$1 million), the KSCIRC group was able to recruit six endowed chairs and several other faculty who have in turn brought in over \$47.1 million in grant funding to the University.

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The Kentucky Spinal Cord Injury Research Center

Philanthropy

Todd Crawford Foundation Supports KSCIRC

On December 20, 2007, a luncheon was held at the UofL Faculty Club where the Todd Crawford Foundation presented a check of support to the KSCIRC. Proceeds came from a run/walk/roll event held June 9, 2007. This year's run/walk/roll event will be held June 28, 2008 at the Waterfront Park. Information can be found at toddcrawfordfoundation.org

Pictured (LR): Christopher B. Shields, M.D., Scott R. Whittemore, Ph.D., Charles H. Crawford, M.D., Bart Brown and Todd Crawford.



Friends for Michael will hold "A Legacy Continues" Dinner and Auction, June 5, 2008. See their web site for events schedule at www.friendsformichael.org FFM is a contributor to the KSCIRC

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.

Name _____

Address _____

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My gift is in Honor of/Memory of (*circle one*):

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.

Please mail this form and your payment to:

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If you have questions or would like more information, please contact Phil Bloyd at (502) 852-0213 or pdboy01@louisville.edu