



**2003 PROGRESS REPORT FOR THE
SPINAL CORD AND BRAIN INJURY RESEARCH CENTER
(SCoBIRC)**

UNIVERSITY OF KENTUCKY

SUBMITTED TO THE

Kentucky Spinal Cord and Head Injury Research Trust

and

the Dean of the University of Kentucky College of Medicine

DECEMBER 31, 2003

EDWARD D. HALL, PH.D.

SCoBIRC DIRECTOR



This report describes our progress in achieving the goals outlined in the 2002 Progress Report. Also presented are related SCoBIRC activities including the Invited Lecture Series and the planning of the 2004 Kentucky Spinal Cord and Brain Injury Research Symposium, a listing of full publications, archived abstracts and new grants for SCoBIRC Faculty and Faculty Associates. Finally, we present the main SCoBIRC goals for 2004.

HIGHLIGHTS OF 2003

- Recruitment of two new SCoBIRC Faculty: Drs. Franca Cambi from Jefferson Medical College and Jinhui Chen from Harvard Medical School.
- Addition of three additional Faculty Associates: Drs. Allan Butterfield, Kurt Hauser and Anna Keller
- Acceptance of four new graduate students into SCoBIRC laboratories: Ying Deng, Vidya Nukala, Matt Garcia and Sarah Pollitt
- Recruitment of three new post-doctoral fellows into SCoBIRC laboratories: Stephanie Nottingham, Jeffrey Bosken and Yanzhang Li.
- SCoBIRC Faculty and Faculty associates published 31 full CNS injury-related publications, 21 archived abstracts and 2 patents or patent applications and delivered 23 invited lecture and seminars at national and international meetings or other universities.
- New CNS injury-related grants attributed to SCoBIRC Faculty and Faculty Associates included 8 NIH R01s (5 awarded plus 3 awaiting Council confirmation), 5 new KSCHIRT grants and 3 grants/contracts from private foundations or industry.
- Eighteen seminar speakers from NIH and various U.S. or Canadian universities participated in the SCoBIRC Seminar Series, including 8 faculty candidates.
- The spinal cord injury gene database "SClgenes" is available on-line.
- Planning has been completed for the 2004 KSCHIRT Symposium

1. PROGRESS RELATED TO 2003 GOALS OUTLINED IN 2002 SCoBIRC PROGRESS REPORT

• RECRUIT ADDITIONAL FACULTY

As noted in the 2002 Annual Report, the UK College of Medicine, upon the recruitment of E.D. Hall as Director, provided SCoBIRC with four additional tenure track core faculty lines to be filled between FY 2004 and 2006. Following an advertisement which appeared in the December 6th issue of **Science**, we received a total of 29 applications. The SCoBIRC Executive Committee (E.D. Hall, Chair, J. Geddes, J. Springer, S. Scheff, G. Smith, G. Klim, J. Hatton-Kolpek, D. Blades) reviewed the applicants, and 8 were invited in for interviews and seminars during 2003.

Recruitment of Dr. Jinhui Chen: An offer was extended to Jinhui Chen, M.D., Ph.D. who has joined us as an Assistant Professor of Anatomy & Neurobiology on December 1, 2003. Dr. Chen who received his degrees from universities in China, has completed two outstanding post-doctoral fellowships in the U.S. during the past 5 years. The first of these was in the laboratory of Dr. Yi Rao at Washington University in St. Louis where Dr. Chen played a key role in the identification of the novel axonal guidance molecules ROBO and SLIT. He then moved on to the laboratory of Dr. Jeff Macklis at Harvard where he worked on the molecular signals associated with the activation of endogenous neurogenesis after reactive oxygen-induced brain injury. Dr. Chen will continue this line of research at UK.

Recruitment of Dr. Franca Cambi: In addition to the Core Faculty recruiting effort, Franca Cambi, M.D., Ph.D. was recruited from Jefferson Medical College in Philadelphia, PA to UK and SCoBIRC. Dr. Cambi, who begins at UK on January 2, 2004 is an expert in neurogenetics and mechanisms of spinal cord disease. She will be an Associate Professor of Neurology and will occupy the endowed SCoBIRC Chair #5. It is anticipated that Dr. Cambi will play a key role in our future translational efforts concerning therapeutics for acute and chronic spinal cord injury.

New SCoBIRC Faculty Associates: Three new faculty associates have been added to the SCoBIRC ranks:

Annadora Bruce-Keller, Ph.D., Assistant Professor of Anatomy & Neurobiology
 D. Allan Butterfield, Ph.D., Professor of Chemistry
 Kurt F. Hauser, Ph.D., Professor of Anatomy & Neurobiology

Ongoing Recruitment of Dr. Kathryn Saatman: An offer has recently been extended to Dr. Kathryn Saatman, currently of the University of Pennsylvania School of Medicine. Dr. Saatman is a well-funded expert in the role of calpain-mediated cytoskeletal damage during post-traumatic brain injury (TBI) secondary damage. If she accepts our offer, she will bring us to a critical mass of expertise in regards to the issue of post-traumatic cytoskeletal degradative mechanisms.

The remaining two SCoBIRC core faculty positions are expected to be filled during the next two fiscal years.

Updated Listing of SCoBIRC Core Faculty and Faculty Associates: The following is an updated listing of our SCoBIRC Core Faculty and Faculty Associates including their research interests (arranged according to Basic-Plasticity/Regeneration/Remyelination, Basic-Neuroprotection and Clinical/Rehabilitation categories).

SCoBIRC Core Faculty:

Edward D. Hall, Ph.D., Director and Professor of Anatomy & Neurobiology, Neurology and Neurosurgery

George M. Smith, Ph.D., Associate Professor of Physiology

James W. Geddes, Ph.D., Associate Professor of Anatomy & Neurobiology

Patrick G. Sullivan, Ph.D., Assistant Professor of Anatomy & Neurobiology

Alexander (Sasha) Rabchevsky, Ph.D., Assistant Professor of Physiology

Jinhui Chen, M.D., Ph.D., Assistant Professor of Anatomy & Neurobiology; started 12/1/2003.

Opening 2-Offered to Dr. Kathryn Saatman, Univ. of Pennsylvania, offer must be accepted by January 23, 2004.

Opening 3-FY 2005

Opening 4-FY 2006

Basic-Plasticity/Regeneration/Remyelination:

Gregory Barnes, M.D., Ph.D., Assistant Professor/Dept Neurology, College of Medicine
Role of axonal guidance molecules in neuronal plasticity and epileptogenesis

Jinhui Chen, M.D., Ph.D., Assistant Professor, Dept. Anatomy & Neurobiology, College of Medicine
Control of post-traumatic neurogenesis

Pamela K. Knapp, Ph.D., Associate Professor/Dept. Anatomy & Neurobiology, College of Medicine
Control of CNS glial development and myelination

Tim McClintock, Ph.D., Associate Professor/Dept. Physiology, College of Medicine
Functional genomics of neuroregeneration and adult neurogenesis

Alexander (Sasha) Rabchevsky, Ph.D., Assistant Professor/ Dept. Physiology, College of Medicine
Interventions to enhance functional recovery and reduce tissue damage following spinal cord injury; role of microglia in modulation of regeneration; mechanisms of autonomic dysreflexia

Stephen Scheff, Ph.D., Professor/Dept. of Anatomy & Neurobiology, College of Medicine; Associate Director, Sanders-Brown Center on Aging
Synaptic plasticity and recovery of function following head trauma and spinal cord injury

George M. Smith, Ph.D., Associate Professor/Dept Physiology, College of Medicine
Cellular and molecular mechanisms involved in CNS wound healing and axonal regeneration; gene therapy of spinal cord injury

Diane Snow, Ph.D., Associate Professor/Dept Physiology, College of Medicine
Neuronal outgrowth inhibitory molecules, specifically chondroitin sulfate proteoglycans (CSPGs) during development and following CNS injury

Basic-Neuroprotection:

Annadora Bruce-Keller, Ph.D., Assistant Professor/Dept. Anatomy & Neurobiology, College of Medicine
Inflammatory mechanisms in traumatic brain injury and neuroprotective effects of estrogen

D. Allan Butterfield, Ph.D., Professor/Dept. Chemistry, College of Arts and Sciences
Role of reactive oxygen mechanisms in neurodegeneration

James W. Geddes, Ph.D., Associate Professor/Dept. Anatomy & Neurobiology, College of Medicine
Cytoskeletal disruption following neuronal insult and calpain as a therapeutic target for spinal cord injury

Edward D. Hall, Ph.D., Professor/Depts. Anatomy & Neurobiology, Neurology, Neurosurgery, College of Medicine
Reactive oxygen and cytoskeletal damage mechanisms in acute CNS injury; pharmacological neuroprotection; gender differences in CNS injury pathophysiology

Kurt F. Hauser, Ph.D., Professor/Dept. Anatomy & Neurobiology, College of Medicine
Role of opiate receptor mechanisms in acute CNS injury

Susan Queen, Ph.D., Assistant Professor, Dept. Rehabilitation Sciences, Division of Physical Therapy
Involvement of glutamate transporters in spinal cord injury, and their potential as a therapeutic target

James Pauly, Ph.D., Associate Professor/Dept. Pharmaceutical Sciences, College of Pharmacy
Pharmacological neuroprotection and cognitive enhancement following traumatic brain injury

Joe E. Springer, Ph.D., Professor/Dept Anatomy & Neurobiology, College of Medicine
Apoptotic cell death in traumatic spinal cord injury

Patrick G. Sullivan, Ph.D., Assistant Professor/Dept Anatomy & Neurobiology
Mechanisms and role of mitochondrial dysfunction in CNS injury

Clinical/Rehabilitation:

Deborah Blades, M.D., Associate Professor/Division Neurosurgery, College of Medicine
The role of trophic factors in recovery from spinal cord injury; spinal cord neurosurgery

Franca Cambi, M.D., Ph.D., Associate Professor/Neurology, College of Medicine; started 1/01/04
Neurogenetics and mechanisms of spinal cord disease

Jody Clasey, Ph.D., Assistant Professor/Dept Kinesiology and Health Promotion
Body composition analysis, and the relationship of body composition measures, physical activity and hormone function

Bernard Fleming, Ph.D., Pre-Service Training Director/Interdisciplinary Human Development Institute
Human factors engineering as applied to job accommodations for people with disabilities; adaptive computer technology

Jimmi Hatton-Kolpek, Pharm.D., Associate Professor/Dept Pharmaceutical Sciences, College of Pharmacy
Organization, design and monitoring of traumatic brain and spinal cord injury trials; clinical pharmacokinetics of neuroprotective agents

Patrick Kitzman, Ph.D., Assistant Professor/Dept Rehabilitation Sciences, Division of Physical Therapy
Neuronal plasticity and spasticity following spinal cord injury.

Gerald Klim, D.O., Associate Professor and Chairman, Dept Physical Medicine and Rehabilitation, College of Medicine and Director, Brain Injury Rehabilitation Program, Cardinal Hill Rehabilitation Hospital
Rehabilitation after traumatic brain injury

Terry Malone, Ed.D., P.T., Professor and Director/Dept Rehabilitation Sciences, Division of Physical Therapy
Sports medicine and orthopedic injuries

Susan McDowell, M.D., Associate Professor/Dept Physical Medicine and Rehabilitation, College of Medicine and Medical Director, Spinal Cord Injury Unit, Cardinal Hill Rehabilitation Hospital
Rehabilitation after spinal cord injury

Philip Tibbs, M.D., Professor/Division of Neurosurgery, College of Medicine
Metastatic cancer of the spine and bone morphogenic protein

Byron Young, M.D., Professor and Head/Division of Neurosurgery, College of Medicine
Clinical trials in traumatic brain injury; cyclosporin A treatment of human TBI

- **RECRUIT ADDITIONAL POSTDOCTORAL RESEARCHERS AND GRADUATE STUDENTS**

With the help of KSCHIRT-provided fellowship funding, we have recruited four new graduate students into SCoBIRC laboratories:

Ms. Ying Deng-laboratory of E.D. Hall
Mr. Matthew Garcia-laboratory of J.W. Geddes
Ms. Sarah Pollitt-laboratory of J.W. Geddes

Mr. Vidya Nukala-laboratory of P.G. Sullivan

In addition, Ms. Stephanie Nottingham has accepted an offer to join the laboratory of E.D. Hall as a KSCHIRT funded post-doctoral fellow after completion of her Ph.D. in the laboratory of J.E. Springer in early 2004. An offer has also been extended to Dr. Jeffrey Bosken who recently completed his Ph.D. at U.K. to join the laboratories of E.D. Hall and S.W. Scheff to work on gas chromatographic/mass spectrophotometric (GC/MS) measurement of isoprostanes (reactive oxygen-mediated lipid peroxidation products) as biomarkers of CNS injury in TBI and SCI models. Yanzhang Li has will join the laboratory of J. Geddes in spring, 2004 after completion of his Ph.D. at Philips Universitat in Marburg, Germany.

- **CONTINUE DEVELOPMENT OF SCI GENE RELATED DATABASE**

The development of the SCI Gene Related Database "SCigenes" is continuing in collaboration with the University of Louisville. The database is available online (<http://scigenes.uky.edu/>). Genes continue to be added, and new on-line search tools are in development.

- **REVISE SCoBIRC WEB PAGE AND BROCHURE**

The SCoBIRC web page has been totally revised and updated and is available on-line (<http://www.mc.uky.edu/scobirc/>). Revision of the SCoBIRC Brochure is in progress.

- **2003 Spinal Cord and Brain Injury Research Center (SCoBIRC) Invited Lecture Series**

January 16

MARY ELLEN MICHEL, Ph.D.

Program Director, National Institutes of Neurological Disorders and Stroke "Opportunities and Challenges for NINDS and Neurotrauma Research"

February 5

OSWALD STEWARD, Ph.D.

Director, Christopher Reeve-Irvine Spinal Cord Injury Research Center
University of California at Irvine

"Use of Mice for Spinal Cord Injury Research: What's Different? What's the Same?" (Co-sponsored with the Department of Physiology)

March 5

LINDA NOBLE, Ph.D.

Professor, Department of Neurological Surgery
University of California, San Francisco

"Vascular Mechanisms Underlying Restoration of Function
After Spinal Cord Injury"

(Co-sponsored with the Department of Physiology)

March 17

TIMOTHY DEVOOGD, Ph.D.

Cornwell University

"Singing in the Brain: Insights into Neural Plasticity Discovered in the Avian song System"

March 24

SHEY-SHING SHEU, Ph.D.

University of Rochester School of Medicine

"Mitochondrial Ca²⁺ Signaling in Neurons & Heart Cells"

(Co-sponsored with the Department of Anatomy & Neurobiology)

March 28

DANA MCTIGUE, Ph.D. (Faculty Candidate)

Ohio State University College of Medicine and Public Health

Chalk talk presentation and group discussion: Myelination and

Oligodendrocyte Progenitors after Spinal Cord Injury

- PHILLIP POPOVICH, Ph.D. (Faculty Candidate)
Ohio State University College of Medicine and Public Health
Chalk talk presentation and group discussion: Neuroinflammatory Mechanisms of Secondary Injury and Repair after Spinal Cord Injury
- April 1
ALAN FADEN, Ph.D.
Georgetown University Medical Center
"Cell Suicide: From Birth to Treating Neurological Disorders"
- April 9
ANDREI KRASSIOUKOV, M.D., Ph.D.
University of Toronto
"Spinal Cord Injury and Changes within Human Spinal Sympathetic Circuits: From Animal Experiments to Clinical Reality"
- April 28
DANXIA LIU, Ph.D. (Faculty Candidate)
University of Texas Medical Branch at Galveston
"Reactive Species and Oxidative Damage in Spinal Cord Injury - The Therapeutic Potential of a Novel Superoxide Dismutase Mimetic Mn (III) Tetrakis (4-Benzoic Acid) Porphyrin"
- June 19
JINHUI CHEN, M.D., Ph.D. (Faculty Candidate)
Harvard Medical School
"Inducing Neurogenesis in Adult Mouse Brain and Determining Neural Stem Cell Fate"
- July 22
JAMES LEE FRANKLIN, Ph.D. (Faculty Candidate)
University of Wisconsin
"Bax, Reactive Oxygen and Cytochrome c Release in Neuronal Apoptosis"
- July 28
ZAVEN KAPRIELIAN, Ph.D. (Faculty Candidate)
Albert Einstein College of Medicine
"Axon Guidance at the Midline of the Developing CNS"
- August 25
KATHRYN SAATMAN, Ph.D. (Faculty Candidate)
University of Pennsylvania
"Cytoskeletal Damage after Traumatic Brain Injury: Implications for Neuronal Structure and Function"
- August 27
RAIMONDO D'AMBROSIO, Ph.D. (Faculty Candidate)
University of Washington School of Medicine
"Posttraumatic Impairment of Brain Extracellular K⁺ Homeostasis: a Role for Glial Cells in Posttraumatic Neuronal Hyperexcitability and Seizures"
- September 8
KEVIN K.W. WANG, Ph.D.
University of Florida
"Biomarkers for Brain injury"
- October 27
HAZEL H. SZETO, MD, Ph.D.
Cornell University Medical College
"Antioxidant peptides targeted to mitochondria prevents permeability transition, cytochrome c release and cell death"
- DEC 1
GARY FISKUM, Ph.D.
University of Maryland School of Medicine
"Mitochondrial Mechanisms of Oxidative Stress in Neurodegeneration"

- **New Grants Awarded to SCoBIRC Faculty**

National Institutes of Health

NINDS RO1 NS045601; **PI: A. J. Bruce-Keller**
 "Estrogen, NADPH Oxidase, and Neurotrauma"
 Direct costs: \$ 925,000, 10/01/03 -05/31/07

NINDS R01 NS ; **PI: J.W. Geddes**
 "Calpain Inhibition Strategies for Spinal Cord Injury"
 Direct costs: \$1,000,000; 01/01/04-12/31/08

NIDA R01 DA15097; **PI: P. E. Knapp**
 "Opiates Modulate Oligodendrocyte Survival and Function"
 Direct costs: \$1,025,000; 05/01/03 to 04/30/07

NIA RO1 AG21981 **PI: S.W. Scheff**
 "Response of the aging nervous system to trauma"
 Direct costs: \$1,250,000, 7/03 – 6/08

NINDS R01 NS **PI: Xiao-Ming Xu, U. Louisville**
 "Schwann cells, neurotrophins, and spinal cord regrowth"
 Direct costs: \$1,000,000; 1/01/04 - 12/31/09
G.M. Smith, sub-contract \$220,470

NINDS R01NS46566; **PI: E.D. Hall**
 "Peroxyntirite-Induced Oxidative Damage in TBI"
 Direct costs: \$1,250,000; 04/01/04-03/31/09

NINDS R01 NS46380 **PI: J.E. Springer**
 "Cyclooxygenase pathophysiology in spinal cord injury:
 Direct costs: \$925,000, 4/01/04-3/31/08.

NINDS R01 NS48191; **PI: P.G. Sullivan**
 "Mitochondrial Uncoupling as a Therapeutic Target in TBI"
 Total Direct: \$1,125,000 2004-2009

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Barnes, G.N.
 "Molecular basis of synaptic reorganization in focal epilepsy"
 Total direct costs: \$300,000; 1/01/03-12/31/06.

Smith, G.M.
 "Isolation of short peptides to neutralize the inhibitory effect of chondroitin sulfate proteoglycans"
 Total costs: \$223,986; 1/1/03 - 12/31/05

Hall, E.D.
 "Novel pharmacotherapy for traumatic brain injury"
 Total costs: \$287,093; 1/15/04-1/14,07

Springer, J.E.

"COX-2 induction in traumatic spinal cord injury"

Total costs: \$253,341; 1/15/04-1/14/07

Rabchevsky, A.G.

"Influence of neurotrophins on intraspinal plasticity modulating autonomic dysreflexia"

Total costs: \$297,000; 1/15/04-1/14/07

Foundations/Industry:**Rabchevsky, A.G.**

American Paraplegia Society Seed Grant

"Growth factor-mediated gene therapy for spinal cord injury"

Total costs: \$16,800; 11/01/03-10/31/04

Rabchevsky, A.G.

Geron Corporation

"Transplantation of human embryonic stem cells into the injured rat spinal cord"

Total costs \$99,730; 1/31/04-6/30/04

Young, AB and Hatton-Kolpek, J.

Pharmos Corporation

"Efficacy and Safety Evaluation of a Single Intravenous Dose of Dexanabinol in Patients Suffering from Severe Traumatic Brain Injury"

6/20/2003-08/27/2004

- **Full Publications by SCoBIRC Faculty:**

Anderson, K.J., Fugaccia, I., and **Scheff, S.W.** Fluoro-jade B stains quiescent and reactive astrocytes in the rodent spinal cord. *Journal of Neurotrauma* 20:1223-1231, 2003.

Bruce-Keller, A.J., A. Chauhan, F.O. Dimayuga, J. Gee, J.N. Keller, and A. Nath. Synaptic transport of HIV-Tat protein causes neurotoxicity and gliosis in rat brain. *J. Neurosci.* 23:8417-8422, 2003.

Bu J, Bruckner SR, Sengoku T, **Geddes JW**, and Estus S . Glutamate regulates caveolin expression in rat hippocampal neurons. *J Neurosci Res* 72: 185-190, 2003.

Candelario-Jalil, E, Gonzalez-Falcon, A., Garcia-Cabrera, M., Alvarez, D., Al-Dalain, S.M., Martinez-Sanchez, G., Leon, O.S., and **Springer, J.E.** The relative contribution of cyclooxygenase isoforms to ischemia-induced oxidative damage and neurodegeneration following transient global cerebral ischemia. *J. Neurochem.* 86:545-555, 2003.

Chauhan, A., J. Turchan, C. Pocerlich, **A.J. Bruce-Keller**, S. Roth, D.A. Butterfield, E.O. Major, and A. Nath. Intraellular HIV Tat expression in astrocytes promotes astrocyte survival but induces neurotoxicity. *J. Biol. Chem.* 278: 13512-9, 2003.

Chouthai N.S., J. Sampers, N. Desai, and **G. M. Smith.** Changes in Neurotrophin Levels in Umbilical Cord Blood from Babies with Different Gestational Age and Clinical Conditions *Pediatric Res.* 53: 965-969, 2003.

Dimayuga, F.O., Q. Ding, J.N. Keller, M.A. Marchionni, K. Seroogy, J, and **A.J. Bruce-Keller**. GGF2, a novel neuregulin, attenuates microglial free radical production. *J. Neuroimmunol.* 136: 67-74, 2003.

Ding Q., E. Dimayuga, S. Martin, **A.J. Bruce-Keller**, V. Nukala, A.M. Cuervo, and J.N. Keller (2003) Characterization of chronic low-level proteasome inhibition on neural homeostasis. *J. Neurochem.* 86:489-97.

Ding Q, K. Reinacker, E. Dimayuga, V. Nukala, J. Drake, **D.A. Butterfield**, J.C. Dunn, S. Martin, **A.J. Bruce-Keller**, and J.N. Keller. (2003) Role of the proteasome in protein oxidation and neural viability following low-level oxidative stress. *FEBS Lett.* 546:228-32.

Garrido, R., **J.E. Springer**, B. Hennig, M. Toborek. Nicotine attenuates arachidonic acid-induced apoptosis of spinal cord neurons by preventing depletion of neurotrophic factors. *J. Neurotrauma* 20(11):1201-1214, 2003.

Gasser M.C., I. Berti, **K.F. Hauser**, R. Fischer-Colbrie, A. Saria. Secretoneurin promotes pertussis toxin-sensitive neurite outgrowth in cerebellar granule cells. *J. Neurochemistry* 85: 662-669, 2003.

Goody, R.J., K.M. Martin, S.M. Goebel, **K.F. Hauser**. Dynorphin A toxicity in striatal neurons via an α -amino-3-hydroxy-5-methylisoxazole-4-propionate/Kainate receptor mechanism, *Neuroscience*, 116: 807-816, 2003.

Guo Z., W Su, Z. Ma, **G.M. Smith**, M.C. Gong. Ca²⁺-independent phospholipase A2 is required for agonist-induced Ca²⁺-sensitization of contraction in vascular smooth muscle. *J. Biol. Chem.* 278:1856-1863, 2003.

Hall, E.D., Detloff, M.R. Johnson, K. Kupina, NC. Peroxynitrite-mediated protein nitration and lipid peroxidation in a mouse model of traumatic brain injury. *J. Neurotrauma* 21:9-20, 2004.

Hall, E.D. Drug development in spinal cord injury: What is the FDA looking for? *J. Rehab. Res. Devel.* 40: 81-91, 2003.

Hynds, DL, Spencer, M, Andres, D, and **Snow, DM** (2003) Rit promotes MEK-independent neurite branching in human neuroblastoma cells. *J. Cell Sci.* 116:1925-1935.

Kupina, N.C., M.R. Detloff, W.F. Bobrowski, B.J. Snyder and **E.D. Hall**. Cytoskeletal protein degradation and neurodegeneration evolves differently in males and females following experimental head injury. *Exp. Neurol.* 180: 55-72, 2003.

Maragos, W.F., D. Tillman, M. Jones, **A.J. Bruce-Keller**, S. Roth, J.E. Bell, and A. Nath Neuronal injury in hippocampus with human immunodeficiency virus transactivating protein Tat. *Neurosci.* 117:43-53, 2003.

Ngo T.B., P.J. Waggoner, A.A. Romero, R.C. Eberhart, K.D. Nelson, and **G.M. Smith**. Poly (l-lactide) microfilaments enhance peripheral nerve regeneration across extended nerve lesions. *J. Neurosci. Res.* 72:227-238, 2003.

Nasr P, Gursahani HI, Pang Z, Bondada V, Lee, J, Hadley RW and **Geddes JW** (2003) Influence of cytosolic and mitochondrial Ca²⁺, ATP, mitochondrial membrane potential, and calpain activity on the mechanism of neuron death induced by 3-nitropropionic acid. *Neurochemistry International* 43: 89-99.

Nottingham, S.A. and **Springer, J.E.** Kainic acid infusions induce caspase-3 activation and cell death of oligodendroglia in rat spinal cord. *J. Comp. Neurol.* 464(4):463-471, 2003.

Pang Z, Bondada V, Zhang SX, Sengoku T, Siman R and **Geddes JW**. Calpain facilitates the neuron death induced by 3-nitropropionic acid and contributes to the necrotic morphology. *J Neuropathol Exp Neurol* 62: 633-643, 2003.

Rabchevsky, A.G., Sullivan, P.G., Fugaccia, I., **Scheff, S.W.** Creatine diet supplement for spinal cord injury: influences on functional recovery and tissue sparing in rats. *J Neurotrauma*, 20, 659-669, 2003.

Regine WF, **Tibbs PA, Young AB,** Payne R, Saris S, Kryscio RJ, Patchell RA. Metastatic spinal cord compression: a randomized trial of direct decompressive surgical resection plus radiotherapy vs. radiotherapy alone. *Int J Radiat Oncol Biol Phys*. 2003. Radiation Oncology, University of Maryland Medical System, Baltimore, MD

Scheff, S.W. and Dhillon, H.S. Creatine-enhanced diet alters levels of lactate and free fatty acids after experimental brain injury. *Neurochemical Research* 29: 469-479, 2003.

Scheff, S.W., Rabchevsky, A.G., Fugaccia, I., Main, J. and Lump, J. Experimental modeling of spinal cord injury: Characterization of a force-defined injury device. *Journal of Neurotrauma* 20:179-193, 2003.

Sensi, S.L., Ton-That, D., **Sullivan P.G.,** Jonas, E.A., Gee, K.R., Kaczmarek, L.K., Weiss J.H., Modulation of mitochondrial function by endogenous Zn²⁺ pools. *Proceeding National Academy of Science*, 100, 6157-6162, 2003.

Snow, DM, Smith, JD, Cunningham, AT, McFarlin, J, and Goshorn EC Neurite elongation on chondroitin sulfate proteoglycans is characterized by axonal fasciculation. *Exp. Neurol.* 182:310-321, 2003.

Sullivan, P.G., Dube, C., Dorenbos, K.D., Steward, O., Baram, T.Z., Mitochondrial uncoupling protein-2 protects the immature brain from excitotoxic neuronal death. *Annals of Neurology*, 53, 711-717, 2003.

Varney K, **Young AB, Hatton J.** A review of albumin usage in the neurosurgical patient. *Pharmacotherapy* 23(1), 15-19, 2003.

Verbois, S.L, **Scheff, S.W., Pauly, J.R.** Chronic nicotine treatment attenuates $\alpha 7$ nicotine receptor deficits following traumatic brain injury. *Neuropharmacology* 44:224-233, 2003.

Verbois, S.L., Hopkins, D.M., **Scheff, S.W., Pauly, J.R.** Chronic intermittent nicotine administration attenuates traumatic brain injury induced cognitive dysfunction. *Neuroscience* 119:1199-1208, 2003.

Zhang SX, Bondada V and **Geddes JW**. Evaluation of conditions for calpain inhibition in the rat spinal cord: effective postinjury inhibition with intraspinal MDL28170 microinjection. *J. Neurotrauma* 20(1):59-67, 2003.

- **Archived Abstracts by SCoBIRC Faculty:**

Bakalkin, G.Y., G. Cebers, Z. Marinova, M. Vlaskovska, A. Nikoshkov, E.E. Colago, U. Hochgeschwender, I.N. Singh, **K.F. Hauser,** T.J. Ekstrm, Y.L. Hurd, V.M. Pickel, T. Yakovleva. Prodynorphin is located in axon terminals and dendrites where its processing is regulated by synaptic activity, *Soc. Neurosci., Abstr.* 889.11, 2003.

Barnes, G.N., K. Hauser, P.E. Schauwecker, **G.M. Smith.** Glutamate receptor activation may modulate transcriptional regulatory proteins of the semaphorin gene family, *Soc. Neurosci. Abstr.* 20:, 2003.

Barnes, G.N., K.F. Hauser, P.E. Schauwecker, G.M. Smith. Glutamate receptor Mediated signaling pathways modulate transcriptional regulatory proteins of the semaphorin gene family during epileptogenesis. American Epilepsy Society Abstracts, 2003.

Dragicevic, N.B., Nukala, V.N., Rabchevsky, A.G., **Sullivan, P.G.**, Characterization of Mitochondria from different Regions of the Rat Spinal Cord. *Journal of Neurotrauma*, 20(10), 1055, 2003.

Gomez-Pinilla, F., Ying, Z., Rathman, A.M., **Sullivan, P.G.** Fasting following traumatic brain injury Compensated for decreases in BDNF and Synaptic Plasticity in the Hippocampus. *Journal of Neurotrauma*, 20(10), 1093, 2003.

Hall, E.D., Detloff, MR, Gibson, TR, Kupina, NC. Peroxynitrite-mediated protein nitration and lipid peroxidation in mouse models of diffuse and focal traumatic brain injury. *J. Neurotrauma* 20(10):1087, 2003.

Hynds, D.L., Badstibner, A., **Snow, D.M.** Inhibition of RhoA signaling increases axon extension on neural chondroitin sulfate proteoglycans. *J Neurotrauma* 20(10):1089, 2003.

Jin, Y., Nottingham, S.A., Maragos, W.F., **Springer, J.E.** Pretreatment with the mitochondrial uncoupling agent 2,4-dinitrophenol (DNP) attenuates oxidative damage and increases tissue sparing in spinal cord injury. *J Neurotrauma* 20(10):1087, 2003.

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- **Patents/Invention Reports by SCoBIRC Faculty:**

Wu, H., J.A. Oostveen, V.H. Sethy, **E.D. Hall**, McCall, R.B. Use of heterocyclic amine-type compounds as neuroprotective agents. U.S. Case# 01395/PRO1

Smith, G.M. Drug releasing biodegradable fiber implant. U.S. #6,596,296

- **Invited Lectures/Seminars by SCoBIRC Faculty:**

Bruce-Keller, A. "NADPH Oxidase and Microglial Signaling."4th Great Lakes Glia Meeting. Thompsonville, MI. September, 2003.

Geddes, JW "Protein Transduction Domains: Possibilities and Problems" National Neurotrauma Society Annual Meeting, Nov 7, 2003, Biloxi, MS.

Hall, ED "Reactive Oxygen Mechanisms in Secondary Brain and Spinal Cord Injury and Antioxidant Strategies", Cambridge Centre for Brain Repair Spring School, Cambridge University, U.K., March 25, 2003.

Hall, ED " Drug Development in Spinal Cord Injury: What is the FDA Looking For?" American Spinal Cord Injury Association, Miami, Florida, April 3, 2003.

Hall, ED "Pathophysiology of Spinal Cord Injury", Symposium on Cellule Staminali e Lesione Midollare: Tra Futuro e Realta (Stem Cell Therapy for Spinal Cord Injury: Present and Future)", Niguardo Hospital, Milan, Italy, May 10, 2003.

Hauser, KF. "Opioid and Non-Opioid Effects of Dynorphin: Implications for CNS Injury" Intl. Narcotics Research Conf. Satellite Symposium, Cadaques, Spain.

Hauser, KF. Organizer and Speaker, Colloquium: "Opioid Peptides: Normal and Pathologic Signaling Mechanisms in Neurons and Glia" American Society for Neurochemistry Annual Meeting, Newport Beach, CA, March, 2003

Hauser, K.F. Symposium, Winter Conference on Brain Research "Cell Death in the Injured CNS: Signaling through endogenous opioids can modulate the survival of oligodendrocytes and neurons", Snowbird, UT, January, 2003.

Hauser, K.F., "Endogenous Opioids: Modulators of CNS Development and Response to Injury". Wayne State University, Dept. Anatomy & Cell Biology

Hauser, K.F. Drug abuse and neural stem cells. Keynote Address Neurochemistry Winter Conference, Sölden, Austria, April 8, 2003.

Hauser, K.F. Co-Organizer with **P.E. Knapp**, Colloquium 11—Opioid system dysfunction in neuroplasticity and in the genesis of disease. May 6th, 2003, Newport Beach, CA; *J. Neurochem.* 85 (Suppl. 1):61 (C10-03).

Hauser, K.F. Co-Organizer with Dr. Toni Shippenberg (NIH, NIDA, IRP), Satellite meeting of the International Narcotics Research Conference (July 6-11) held in Perpignon, France. Pathophysiological non-opioid effects of dynorphins: Implications for Stroke, Chronic Pain, and Nerve Injury, July 4th-6th, 2003.

Rabchevsky, AG. "Gene therapy for spinal cord dysfunction," University of California at Irvine, Department of Anatomy & Neurobiology and the Reeve-Irvine Research Center *Spinal Cord Injury Techniques Course* lecture series, July, 2003

Rabchevsky, AG. "A surgically implanted neuroprosthesis for exercise, standing, and transfers after SCI," University of California at Irvine, Department of Anatomy & Neurobiology and the Reeve-Irvine Research Center. *Spinal Cord Injury Techniques Course* lecture series, July, 2003.

Rabchevsky, AG. "Bowel and Sexual Dysfunction after Spinal Cord Injury. *Autonomic Dysfunction after Spinal Cord Injury: Mechanisms, Prevention and Treatment Symposium*," Banff, Alberta, Canada. July, 2003.

Smith, GM "Regeneration and Guidance of Sensory Afferents" Kentucky Spinal Cord Injury Research Center, Neurological Surgery, Louisville, KY, February 20, 2003.

Smith GM "Isolation of short peptides to neutralize the inhibitory effect of chondroitin sulfate proteoglycan". *Frontiers in Spinal Cord Regeneration Symposium*, Louisville, KY; June 26, 2003.

Smith, GM "NGF regulates semaphorin3A chemorepulsion of primary nociceptive afferents *in vitro* and in the adult spinal cord." International Brain Research Organization, Prague, Czech Republic; July 15, 2003.

Smith GM "Growth and guidance factors modulating nociceptive afferent sprouting within the adult spinal cord." International Symposium on Neural Regeneration, Asilomar, CA; December 12, 2003.

Snow, DM "Mechanisms of Inhibition by Chondroitin Sulfate Proteoglycans: the role of growth factors" University of Wales, United Kingdom, May 2003.

Snow, DM "Mechanisms of Chondroitin Sulfate Proteoglycan Inhibition of Nerve Growth" Center for Spinal Injuries, Oswestery, Shropshire, England, June 2003.

Snow, DM "Chondroitin Sulfate Proteoglycan Inhibition is Growth-Factor Dependent", 3rd International Conference on Proteoglycans, Parma, Italy, Sept. 2003.

Snow, DM "Extracellular Matrix Molecules as Regulators of Generation and Regeneration", University of Louisville - Kentucky Spinal Cord Research Center, Neurology Grand Rounds, September 16, 2003.

2. SCoBIRC GOALS FOR 2004

- **RECRUIT ADDITIONAL FACULTY**

We hope to complete the recruitment of Dr. Kathryn Saatman during the current fiscal year, and to pursue the filling of opening #3 during FY 2005. We currently have three excellent candidates being considered for this opening.

- **CONTINUE TO BUILD EXTRAMURAL FUNDING BASE**

It is our continuing goal to enhance the funding base of SCoBIRC particularly in regards to Federal support. This will be pursued with several new R01, R21 and other NIH applications by Core Faculty and Faculty Associates. Each of these will seek to take advantage of logical opportunities for collaboration among SCoBIRC faculty irregardless of department affiliation and whether prospective co-investigators are in different colleges within the University of Kentucky. In addition, we will continue planning for submission of one or more PPG or center grant applications during the coming year. Possible research foci of those applications that are under discussion include reactive oxygen mechanisms, calpain-mediated cytoskeletal damage and mechanisms of autonomic and sensory dysfunction in SCI. In each of these instances, we have a critical mass of research expertise that we can leverage.

- **PURSUE OPPORTUNITIES FOR BASIC-CLINICAL TRANSLATION**

Biomarker Development: An important part of the SCoBIRC mission is to translate basic science discoveries concerning the pathophysiology and treatment of SCI and TBI into improvements in clinical care. During the coming year, we will continue to identify areas of research where the opportunities for basic-clinical translation are most realistic. As a first effort, we are setting up methods for measurement of the family of lipid peroxidation products known as "isoprostanes" which show promise as a biomarker for monitoring of the secondary pathophysiology of CNS injury. We have purchased a new GC-MS, using both College of Medicine and KSCHIRT grants funds, and have recruited a post-doctoral fellow with GC-MS experience. His efforts during 2004 will involve setting up the published isoprostane measurement methods and analyzing CNS tissue and biofluid levels of isoprostanes in our animal models of TBI and SCI. In late 2004 or early 2005, we hope to be ready to utilize this methodology to measure isoprostanes in biofluids from severely injured UK TBI patients. The development of this and other biomarkers is critically important to allow us to monitor the time course and severity of secondary injury mechanisms and the effects of novel neuroprotective agents in future clinical trials.

Cyclosporin A Neuroprotection for TBI: SCoBIRC faculty members S. Scheff and P. Sullivan have previously demonstrated the neuroprotective pharmacology of the immuno-suppressive agent cyclosporin A (CsA) in rodent models of TBI including dose-response, therapeutic window and mechanism of action. These studies inspired an ongoing NIH-funded UK Phase II clinical trial of CsA pharmacokinetics in severe TBI patients that is being lead by Drs. B. Young and J. Hatton-Kolpek. During the coming year, SCoBIRC basic and clinical faculty will work closely to address additional basic research and clinical bioanalytical questions that are necessary in order to lay the necessary groundwork for later phase CsA clinical trials. In addition, SCoBIRC faculty J. Springer, P. Sullivan and E. Hall are currently evaluating the neuroprotective effects of non-immunosuppressive analogs of CsA and FK-506 in TBI and SCI models to see if the immunosuppressive effects of these agents, which are unrelated to the neuroprotective action, can be eliminated. Such non-immunosuppressive compounds would obviously be safer for clinical use.

Potential Use of High Dose Methylprednisolone in TBI: At present, high dose methylprednisolone therapy is the standard of care for acute SCI treatment. We (E. Hall, P.

Sullivan, S. Scheff) have initiated studies in our rodent TBI models to evaluate whether identical treatment will be useful and safe for acute TBI. These studies include an evaluation of whether certain the non-glucocorticoid analogs of methylprednisolone might duplicated the steroid's neuroprotective effects without the potential for adverse reactions. If these studies are positive, phase II studies of high dose methylprednisolone in severe TBI patients will be pursued here at UK.

- **Host 2004 KSCHIRT SYMPOSIUM**

We will host the 2004 KSCHIRT Symposium on June 10-11, 2004 at the Keeneland Race Course. The planning committee consisting of J. Geddes, D. Snow, G. Smith, P. Sullivan, A. Rabchevsky and E. Hall (Chair) has completed the program and all invited speakers have accepted (see attached announcement).