# Dr. Edward Hall Director Spinal Cord and Brain Injury Research Center University of Kentucky



#### **Neurotrauma Research Centers in Kentucky**

 University of Kentucky Spinal Cord & Brain Injury Research Center (SCoBIRC)

University of Louisville-Kentucky Spinal Cord Injury Research Center (KSCIRC)

Both inspired by the creation of the Kentucky Spinal Cord & Head Injury Research Trust

Brainchild of State Senator Tim Shaughnessy

## **KY State Senator Tim Shaughnessy**

Father of the Kentucky Spinal Cord & Head Injury Research Trust Fund



- D-Louisville (part of Jefferson County)
- Member of Senate since 1989
- Served as Chairman of the Education Committee
   and several other committees
- One of Senate's greatest champions of education and has played a leadership role in elevating The University of Kentucky and University of Louisville to national prominence as research institutions
- Up for re-election in 2008
- Day job: Corporate VP, Jewish Hospital, Louisville
- Motivating Interest in Neurotrauma Research: niece Maggie, while in high school in early 90s, became a quadriplegic following a car accident

# KSCHIRT

- <u>Spinal</u> <u>Cord</u> and <u>Head</u> <u>Injury</u> <u>Research</u> <u>Trust</u> fund established by KRS 211.504
  - Revenues received from the additional penalties imposed on speeding violations (\$12.50) [KRS 189.394(5)], violations of the mandatory seat belt law (\$10.00) [KRS 189.125], and driving under the influence (\$15.00) shall be credited to KSCHIRT
- Federal funds or other funds may supplement or match state funds
  - Funds shall be used to finance the spinal cord and head injury research programs at the University of Kentucky or University of Louisville Effective: July 15, 1994









#### **SCoBIRC Leadership**

Edward D. Hall, Ph.D. Director

James W. Geddes, Ph.D. Associate Director

Patrick G. Sullivan, Ph.D. Associate Director

Ms. Zelneva M. Frye Center Administrator

Ms. Mary E. (Liz) Jones Administrative Associate

> Byron Young, M.D. Clinical Director



Professor of Neurosurgery Director, KY Neuroscience Institute Johnston-Wright Endowed Chair of Surgery



#### SCoBIRC Leadership (continued)



Joe E. Springer, Ph.D.

Cardinal Hill Endowed Chair in Neurorehabilitation Professor and Vice Chair for Research, Department of Physical Medicine & Rehabilitation

#### **SCoBIRC Mission Statement**

The Spinal Cord and Brain Injury Research Center (SCoBIRC) at the University of Kentucky College of Medicine was established in 1999 to promote both individual and collaborative studies on injuries to the spinal cord and brain that result in paralysis or other loss of neurologic function.

#### The mission of the Center is to:

•Enhance the understanding of the acute pathophysiology of CNS injury and mechanisms that regulate neuronal plasticity, axonal guidance and myelination.

- Identify biomarkers that can be used to track post-traumatic pathophysiology and the effects of neuroprotective and neurorestorative treatments
- •Help identify innovative clinical trial methodologies and therapeutic endpoints
- Improve the use of rehabilitation strategies to maximize treatment effects

•Discover, translate and develop pharmacological, gene therapy or cellular treatments to minimize damage, promote repair mechanisms and enhance regeneration and remyelination following spinal cord or brain injury.

# Annual New Cases of SCI\*

- U.S.A. 11,000
- Canada 1,500

15,200

- Western Europe
- Japan 5,500
- Australia & New Zealand 1,250
- \* "Facts and Figures at a Glance" National Spinal Cord Statistical Center Birmingham, Alabama May, 2001

## Most SCIs do not involve transection of the spinal cord

spinal cord injury



**Mechanism.** Vertical blow on head as in diving or surfing accident, being thrown from car, or football injury







Burst fracture with characteristic vertical fracture through vertebral body

X-ray film showing fracture of C5



More severe trauma explodes vertebral body. Posteriorly displaced bone fragments frequently produce spinal cord injury

X-ray film showing fracture of C6



#### Pathophysiology of Acute Spinal Cord Injury

**Primary Injury** - Mechanical shearing of axons and blood vessels

 Secondary Injury - Microvascular and neuronal injury due to a cascade of pathophysiological events that exacerbate primary injury. (Potential target of pharmacological treatment)

# **Time Course of Post-traumatic Spinal Cord Degeneration** cross section of the normal spinal cord 3 to 5 minutes after SCI several weeks after SCI 15 to 30 minutes after SCI

#### Methylprednisolone Sodium Succinate



## **The New England Journal of Medicine**

Copyright, 1990, by the Massachusetts Medical Society

Volume 322

May 17, 1990

Number 20

#### A Randomized, Controlled Trial of Methylprednisolone or Naloxone in the Treatment of Acute Spinal-Cord Injury

**Results of the Second National Acute Spinal Cord Injury Study** 

Michael B. Bracken, Ph.D., Mary Jo Shepard, M.P.H., William F. Collins, M.D., Theodore R. Holford, Ph.D., Wise Young, M.D., David S. Baskin, M.D., Howard M. Eisenberg, M.D., Eugene Flamm, M.D., Linda Leo-Summers, M.P.H., Joseph Maroon, M.D., Lawrence F. Marshall, M.D., Phanor L. Perot, Jr., M.D., Joseph Piepmeier, M.D., Volker K.H. Sonntag, M.D., Franklin C. Wagner, M.D., Jack E. Wilberger, M.D., and H. Richard Winn, M.D.

## NASCIS 2 Effect of Methylprednisolone on Motor Function

#### When Administered Within 8 Hours of Injury



## Annual U.S. Epidemiology of Traumatic Brain Injury (TBI)

Total TBIs = 1,578,000

Number seeking medical care = 1,200,000

- Patients admitted to hospital with:
  - Severe TBI = 58,000
  - Moderate TBI = 64,000
  - Mild TBI = 155,000
- Numbers for Europe are similar

# Brain Injury is a Mechanical Event

![](_page_16_Picture_1.jpeg)

#### Severe TBI: Hematomas → Ischemic Edema and Herniation

![](_page_17_Figure_1.jpeg)

![](_page_17_Figure_2.jpeg)

![](_page_17_Picture_3.jpeg)

FIG. 63.4. Acute subdural hematoma. Noncontrast axial computed tomography demonstrates a hyperdense, crescent-shaped, extraaxial collection showing mass effect (sulcal and ventricular effacement) and midline shift from left to right. (Courtesy of Drs. J.A. Bello and S.K. Hilal.)

From Chapter 14, Greenfield's Neuropathology, 7th Ed.

![](_page_18_Picture_0.jpeg)

![](_page_19_Figure_0.jpeg)

![](_page_20_Picture_0.jpeg)

![](_page_20_Picture_1.jpeg)

Jim Geddes

![](_page_20_Picture_3.jpeg)

![](_page_20_Picture_4.jpeg)

![](_page_20_Picture_5.jpeg)

George Smith

# **SCoBIRC Core Faculty**

- Pharmacological treatments for acute brain and spinal cord injury
- Secondary neurodegeneration after spinal cord and brain injury, focusing on the protease calpain
- Role of mitochondrial dysfunction in the neuropathology of brain and spinal cord injury
- Mechanisms by which axons fail to regenerate after injury to the brain or spinal cord
- Promoting regeneration by inhibition of glial scar formation after brain or spinal injury
  - Role of specific cytoskeletal proteins in damage and recovery from traumatic brain injury
  - Gene therapy and molecular biological approaches for treatment of spinal cord injury
- Somatosensory circuit disruption and rehabilitation after mild to moderate diffuse traumatic brain injury

![](_page_20_Picture_16.jpeg)

**Diane Snow** 

![](_page_20_Picture_18.jpeg)

![](_page_20_Picture_20.jpeg)

Kathy Saatman Sasha Rabchevsky Jonny Lifshitz

# **SCoBIRC** Faculty Associates

- Anatomy & Neurobiology
  - Stephen M. Onifer, Ph.D.
  - Stephen W. Scheff, Ph.D.
  - Indrapal N. Singh, Ph.D.
  - Diane M. Snow, Ph.D.
  - Physiology
    - Rodney P. Guttmann, Ph.D.
  - Neurosurgery
    - Karin R. Swartz, M.D.
    - Byron Young, M.D.
  - Neurology
    - Franca Cambi, M.D., Ph.D.
  - **Biological Sciences** 
    - Randal S. Voss, Ph.D.
  - Kinesiology and Health Promotion
    Jody Clasey, Ph.D.

- Pharmaceutical Sciences
  - Jimmi Hatton-Kolpek, Pharm.D.
  - Kimberly Nixon, Ph.D.
  - James R. Pauly, Ph.D.
- Physical Medicine & Rehabilitation
  - Walter M. High, Ph.D.
  - Gerald Klim, D.O.
  - Susan McDowell, M.D.
  - Melanie L. McEwen, Ph.D.
  - Joe E. Springer, Ph.D.
- Rehabilitation Sciences
  - Richard D. Andreatta, Ph.D.
  - Patrick H. Kitzman, Ph.D.
  - Terry Malone, Ed.D., P.T.
- Psychology
  - Mark A. Prendergast, Ph.D.
  - Michael T. Bardo, Ph.D.
- Communication Disorders
  - Kathleen M. Youse, Ph.D.

## **Current SCoBIRC Research Strengths**

- Acute Neuroprotection pharmacological inhibition of secondary injury after SCI and TBI
  - Oxidative damage
  - Calcium-mediated damage
  - Mitochondrial damage and metabolic failure
- Promotion of Axonal Sprouting and Regeneration and Synapse Formation
  - Gene delivery of growth factors to promote growth and target guidance
  - Counteraction of astrocyte and oligodendrocyte-derived inhibitory factors
- Reduction of post-SCI spasticity, neuropathic pain and autonomic dysreflexia
  - Inhibition of abnormal sensory axonal sprouting
  - Selective pharmacological inhibition of sensory neurotransmitter release

#### Define pathophysiology of mild TBI→identify treatment strategies

#### **Current SCoBIRC Translational Projects**

#### Cyclosporine A (CsA) for Severe TBI

- Basic research of Sullivan and Scheff (1997-2000) showing protective effects of CsA in rodent TBI models based upon mitochondrial functional preservation
- Phase I/IIa Evaluation of cyclosporin A in severe TBI -Young/Hatton-Kolpekcompleted
  - Planning grant for Phase III Multicenter Clinical Trial-Young/Hatton-Kolpek

#### Biomarker studies in severe TBI -Hall/Hatton-Kolpek/Young

- Oxidative damage
- Cytoskeletal degradation

#### Novel neuroprotective agents in preclinical testing

- Mitochondrial protective agents
- Non-immunosuppressive CsA analogs-NIM811
- Calpain inhibitors
- Dual lipid peroxidation inhibitors/peroxynitrite scavengers
- Novel subtype selective NMDA receptor antagonists
- Combination strategies

## Evaluation of glutamate release inhibitor gabapentin in SCI spasticity and autonomic dysreflexia

![](_page_24_Picture_0.jpeg)

![](_page_24_Picture_1.jpeg)

UK