Center for Aging and Brain Repair

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Mission Statement

The mission of the Center of Excellence for Aging and Brain Repair is to develop new therapeutic strategies to promote repair and regeneration of aging and diseased brain. Building on a foundation of excellence in basic and clinical research, we focus on translating innovative ideas into industrial partnerships, educational and clinical services to address key needs of the community and those suffering from brain injury and disease.
Center of Excellence for Aging and Brain Repair

- Internationally Recognized as a Top Research Center at USF
- Well Known as Leader and Innovator in Adult Stem Cells
- Significant Extramural Funding/License/ Royalty Income
- High number of Publications, Patents and Spin Out Companies
- Excellent Public Relations and Media Coverage
- Headquarters for National Society
- Editorial Office for Two International Journals
Center of Excellence for Aging and Brain Repair Team Members

• Core Faculty
• Highly cited in Scientific Literature
• Significant involvement in Federal, State and Foundation Peer Review Panels
• 1 PPG, 3 RO1s, 2 R21s, 1 R41, Foundation and Industry Support
• Dr. Paula Bickford – Nutritional Neuroscience
• Dr. Nagwa Dajani – Hematopoietic Immunology - Education
• Dr. Denis English – Vascular Stem Cells – Editor, Stem Cells & Development
• Dr. Tom Freeman – Clinical Neurosurgery Trials
• Dr. Svitlana Garbuzova-Davis – Transgenic Models/Spinal Cord
• Dr. Linella Gemma – Nutritional Neuroscience and neuroimmunology
• Dr. Ron Mervis – Structural Plasticity of Brain
• Dr. Paul Sanberg – Adult Stem Cells, Editor, Cell Transplantation
• Dr. Andreas Seyfang – Neuroimmunology and Bacteriology
• Dr. Doug Shytle – Small Molecule Development Psychopharmacology
• Dr. Alison Willing – Cell Therapy for Stroke/Parkinson’s
• Dr. Wes Johnson – Spinal Cord
Past Five Years

- Center Established from Dept. of Neurosurgery – Dr. David Cahill
- Significant Growth of Faculty, Collaborations and Extramural Funding
- Intimately involved with neurosurgery/neurology/psychiatry translational research
- Publications - >150 publications since 2000 (~25-30/yr)
- Intellectual Property - Disclosures & Patents >20 – 3 Spin-out Companies – Significant license revenue brought in.
- Public Relations – Significant Positive Impact
- Novel Education Programs – Grad. Certificates – Ph.D. program
Paula Bickford, Ph.D., a researcher at the University of South Florida Center of Excellence for Aging and Brain Repair, is particularly interested in the role of antioxidants in brain health. The brain is a good place to study the benefits of antioxidants because it has one of the highest percentages of fats of any organ in the body, and it is in our fats that free radicals inflict much of their damage. As we age, “communications between neurons become damaged, kind of like what happened to the Tin Man in the Wizard of Oz,” she explains. “Oxidative damage caused the Tin Man to grow rusty—until Dorothy came along and oiled him.” Similarly, antioxidants help to “regrease the lines of communication” in the cells in our brain, says Bickford.

Professor Paul Sanberg, of the University of South Florida, took stem cells - progenitor cells that can become other types of cell - from the blood of umbilical cords.

**Targeting the saints, not the sinners?**

*STATE Edition*
St. Petersburg Times - St. Petersburg, Fla.
SUSAN ASCHOFF
Mar 23, 2006

We want to believe we can outwit disease. We eat whole grains and teetotal and run for our lives in one place on treadmills. Yet recent research suggests straight arrows - the personality types who don't drink or smoke, who drive the speed limit and arrive on time for appointments -
The objective of the Graduate Certificate in Aging and Neuroscience is to provide training for talented students in the rapidly growing field of Neuroscience, and to meet the demands of the increasingly aging population. The certificate is offered by the Center of Excellence for Aging and Brain Repair, the Department of Neurosurgery, USF. Faculty members of the center are world class authorities in the fields of Aging and Neuroscience. The students will have the opportunity to be closely mentored by faculty members in both a lecture-style classroom setting and bench-top research.

Neuroscience is one of the signature programs at the University of South Florida College of Medicine. The program combines fundamental courses of neuroanatomy, physiology, molecular biology and pathology, as well as applied research - particularly cell therapy to disorders of the CNS. In addition, students are offered several electives that cater to their special interests such as laboratory rotations, directed research, and special topics. Special emphasis is given to diseases of the aging population including Alzheimer's and Parkinson's disease.

www.outreach.usf.edu/gradcertsla
Current Budget

- State Funds ~ Center & SCI ~ $884,689 Personnel 88%
- Extramural Funds > 2 million/year leverage 3:1 ratio
- Extramural Funds ~ other departments – NASA, STTR, Merit
- HRSA Construction Funds ~ 7 million/3yrs (move in Nov. 2006)
- Industry Rebate and Philanthropy $1.2 million
- Most Faculty 0.5 FTE or Lower
- Low Junior Faculty Salaries
Major Neurological Diseases

- Parkinson’s Disease
- Stroke
- Traumatic brain injury
- Spinal cord injury
- ALS
- Other neurodegenerative disorders (e.g. Alzheimer’s Disease)
Center of Excellence for Aging and Brain Repair

Therapeutic Strategies

- Cell Therapy Programs
  - hNT Neurons
  - Fetal Tissue
  - Sertoli Cells
    - Stem Cells
      - Embryonic
      - Bone Marrow
  - Umbilical Cord Blood

- Small Molecules Program
  - Antioxidants
  - Growth Factors
    - Immuno-suppressants
  - Nicotinic Receptor Antagonists
    - Nutraceuticals
## Technology Development Timeline

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nicotinic Antagonist</strong></td>
<td>(small molecule)</td>
</tr>
<tr>
<td>Inversine® (Hypertension) – Targacept, Inc.</td>
<td>On Market</td>
</tr>
<tr>
<td>Inversine (Depression)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Mecamylamine Isomers</td>
<td>Preclinical</td>
</tr>
<tr>
<td><strong>hNT Cells – Stroke Technology</strong></td>
<td>LBS Technologies, Inc.</td>
</tr>
<tr>
<td></td>
<td>Phase IIB Dose Study</td>
</tr>
<tr>
<td><strong>Sertoli Cell- (Immunosuppresant Cell Therapy)</strong></td>
<td>Preclinical</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td><strong>Cord Blood Stem Cells</strong></td>
<td></td>
</tr>
<tr>
<td>Heart Ischemia</td>
<td>Large Animals</td>
</tr>
<tr>
<td>ALS</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Sanfillipo</td>
<td>Discovery</td>
</tr>
<tr>
<td><strong>Nutraceuticals - Dietary Supplements</strong></td>
<td>In Development (2006)</td>
</tr>
<tr>
<td>Stem Cell Augmentation</td>
<td></td>
</tr>
<tr>
<td>Antioxidants</td>
<td>In Development</td>
</tr>
</tbody>
</table>
Stroke

- 4 million survivors in USA
- Leading cause of adult disability
- ~750,000 strokes in USA/year
- Annual cost > $43 Billion
- Standard treatment
  - tPA
  - Rehabilitation
Ischemic stroke

Area of damage

Carotid artery

Plaque

Thrombotic blood clot
Stroke Program

- No reasonable therapy available
- Need regenerative medicine therapy

**Chronic Stroke**
- Neural progenitor cells – LBS Neurons
- Completed – Phase IIB
- Issued & Submitted Patents (with Univ. Penn.)

**Acute Stroke**
- Umbilical cord blood stem cells
- Preclinical – Undergoing pilot GMP Manufacturing
- Numerous Patent Applications
hNT Neurons

Cultured Human Neurons from STRATAGENE

- elaborate processes typical of mature postmitotic human neurons
- express many neuronal markers
- express functional NMDA and non-NMDA glutamate receptor channels
- express and secrete amyloid precursor peptides
- can be transplanted into rodent brains
- are permissive for HIV infection
- can be transplanted

Call Stratagene at 1-800-424-4444
for information about placing standing orders and volume discounts.

hNT Neuron EH
Catalog #304100
N2 Precursor Cells
Catalog #304101

Making Life Better™
NT2 cells
- derived from a human teratocarcinoma
- grown in large numbers
- no neuronal phenotype

NT2N neurons
- Differentiated with retinoic acid
- Postmitotic neurons
- Immature neuronal phenotype
University of Pittsburgh surgeon Douglas Kondziolka injects the Layton BioScience cells into Cerasini's brain.
Injection of LBS-Neurons into Brain of Stroke Patient

Post-Injection Assessment of LBS-Neurons (4 and 24 weeks after transplant)
Stem Cells

• Stem cells exhibit proliferation, self-renewal, and generate a large number of progeny
• Pluripotent: differentiate into any cell type
• Types of Stem Cells
  – Embryonic
  – Adult
Umbilical Cord Blood Stem Cells (hUCB)
Advantages of Cord Blood

• No risk to mother or child
• Non-invasive collection
• Low immunogenicity
• Increased proliferation
• Young cells; long telomeres
Expression of Neural Markers in hUCB


TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>DMEM Treatment</th>
<th>RA + NGF Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musashi-1 ir cells per field</td>
<td>1.50 ± 0.47</td>
<td>4.6 ± 1.02</td>
</tr>
<tr>
<td>Total cells (phase contrast)</td>
<td>93.9 ± 5.35</td>
<td>74 ± 8.53</td>
</tr>
<tr>
<td>% of Total</td>
<td>1.5</td>
<td>6.2</td>
</tr>
<tr>
<td>β-Tubulin-ir cells per field</td>
<td>23.0 ± 8.82</td>
<td>9.02 ± 1.72</td>
</tr>
<tr>
<td>Total cells (phase contrast)</td>
<td>289 ± 13.44</td>
<td>48.2 ± 1.36</td>
</tr>
<tr>
<td>% of Total</td>
<td>8.0</td>
<td>18.7</td>
</tr>
<tr>
<td>GFAP-ir cells per field</td>
<td>88.7 ± 8.50</td>
<td>34.7 ± 3.42</td>
</tr>
<tr>
<td>Total cells (phase contrast)</td>
<td>255 ± 7.46</td>
<td>52.4 ± 2.06</td>
</tr>
<tr>
<td>% of Total</td>
<td>34.7</td>
<td>66.2</td>
</tr>
</tbody>
</table>

FIG. 1. Immunocytochemical identification of neural progenitor cells. (A) NGF + RA-treated culture immunostained for Musashi-1. (B) DMEM-treated culture stained for Musashi-1. (C) NGF + RA-treated culture immunostained for β-tubulin-III. (D) NGF + RA-treated culture, primary delete control. (E) NGF + RA-treated cultures immunostained for GFAP.
Intravenous Administration of Human Umbilical Cord Blood Reduces Behavioral Deficits After Stroke in Rats

Jieli Chen, MD; Paul R. Sanberg, PhD; Yi Li, MD; Lei Wang, MD; Mei Lu, PhD; Allison E. Willing, PhD; Juan Sanchez-Ramos, PhD; Michael Chopp, PhD
Stroke and hUCB Stem Cells

Optimal Time Post-Stroke for MNC Transplantation

- MCAO only
- 3 hr
- 24 hr
- 48 hr
- 72 hr
- 7 d
- 30 d

Ipsilateral Hemisphere Compared to Contralateral Hemisphere

- MCAO only
- 3 hr
- 24 hr
- 48 hr
- 72 hr
- 7 day
- 1 month

Fluorojade
Proposed Mechanism of Repair

Brain → MCAO → Neurodegeneration

↑ Inflammation
↓ Blood Brain Barrier

HUCB

Growth Factors
Angiogenic Factors
Cytokines

Brain → MCAO → Neurodegeneration / ↑ Neurogenesis

↓ Inflammation (↓TNFα, ↑IL-10)

↑ Angiogenesis / Restoration of Blood Flow (↑VEGF)
Reproducibility of HUCB Effects

STROKE

TRAUMATIC BRAIN INJURY

SPINAL CORD INJURY

AMYOTROPHIC LATERAL SCLEROSIS

OTHER CONDITIONS
Next 1 to 5 Years

- Move into new facility (2006-2007)
- Purchase Equipment
- Bring 2 highly funded collaborative researchers on board
- Hire Lab Manager – Knowledge
- Get everyone Federally Funded (Collaborative Research)
- Federal Disease Specific Cell Bank Contracts
- Autologous Cell Storage Clinical Service – Hematopoetic, Adipose & Tooth Pulp Stem Cells
  - Use Industry Rebate Funds to seed lab (500,000)
  - Develop Profit Center Business Plan (2006-2007)
- Ph.D. Faculty to be PI of Clinical Studies
- Increase Philanthropy – Name the Center
- Publish in Higher Impact Journals
- Increase Positive Press – Awards to Faculty
- Increase involvement in Novel Educational model – Self-Sustaining Budget
- Be the Premier National Brain Repair Institute
STRIVE FOR NATIONAL PROMINENCE
Internationally Recognized as a Top Research Center at USF
Approved State of Florida Type II Research Center
Well Known as Leader and Innovator in Adult Stem Cells
Significant Extramural Funding
Significant License/ Royalty Income
Significant Publications,
Licensed Patents,
Positive Media Coverage
Spinout Companies
Headquarters for National Society
Editorial Office for Two International Journals

RESEARCH REALLY MATTERS
• Top University Center for Translational Research
• Promotes Creative Entrepreneurial Research Model
• Highly qualified and productive faculty members
  (15 Core, 11 Affiliated)
• Faculty are highly cited in the scientific literature
  • The Center is a HSC Research Core
  • Studies Important Diseases
• Focus on Cell Therapy/ Small Molecules Development for
  brain & heart repair

TRUE COLLABORATION:
COM & HSC & UNIVERSITY
• True Interdisciplinary Center
• Affiliated with numerous HSC Colleges and Departments
• Affiliated with Other USF Units Including:
  • USF Collaborative on Aging
  • Psychology & Biology Depts.
• Biomedical Engineering and Nanotechnology
• USF Neuroscience Signature Program
• USF Center for Entrepreneurship

CREATIVE PRACTICE MODELS
• Translational Scientists interacting with Physician Scholars
• Success in Developing Novel Therapeutics for Specialty Clinics and Pharma/Biotech trials
• Affiliated with Numerous Clinical Research Units

CREATIVE EDUCATIONAL MODELS
• Taking the Lead in Developing Novel Education Programs
• Ph.D. Program in Aging & Neurosciences
• Graduate Certificates & Master for Medical Professionals
• Distance Learning Programs in Clinical Research
• Established Researchers Teaching Students

USF Center of Excellence for Aging & Brain Repair
Neurosurgery—USF Brain Health—College of Medicine—USF Health