

NeuroBiotechnology Program Of Louisiana...

Putting Ideas To Work For Louisiana



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Program Description

The Neurobiotechnology Program of Louisiana was established in 2002 by a Louisiana Legislative appropriation. The purpose of the program is to strengthen multi-disciplinary research, effective means of cooperation, and core resources among Louisiana universities for the purpose of developing a neurobiotechnology industry. The overall excellence and innovation in the neurosciences at these institutions will promote the discovery of new drug targets and novel therapeutic compounds and thereby address the burden of neurological and psychiatric diseases.

Mission

- To establish a state-wide, transuniversity alliance in neuroscience to capitalize on the state's emerging excellence in neuroscience in order to create the "critical mass" needed to foster the development of a neurobiotechnology/ pharmaceutical industry in the state.
- To develop trans-university core infrastructure and core facilities to provide support to investigators, and to facilitate interactions and collaborations.
- To establish a consortium that will be a magnet for attracting pharmaceutical companies, their subsidiaries, or start-up companies to the state.

Vision

Large pharmaceutical companies have become, largely through mergers, huge corporate giants with multilayered managerial structures that have relatively slowed the decision-making process in drug development and discovery. At the same time, the drug-discovery pipelines are not plentiful. The **Neuro-biotechnology Program** will foster the birth of start-up companies, and the initiative itself will become a magnet to attract branches of existing large pharmaceutical/ biotechnology companies to Louisiana. Overall these will contribute to the creation of a new culture of innovation, and will result in tangible economic development.

Targets

Alzheimer's disease Stroke Head injury Drug addiction

Learning disabilities Pain Hearing problems Stress

Neuropsychiatric abnormalities Retinitis Pigmentosa Age-Related Macular Degeneration

Diabetic Retinopathy Glaucoma

Overview

The Tulane and LSU (New Orleans and Shreveport) Health Sciences Centers have created a partnership by bringing scientists together and serving as the catalyst for the planning and implementation of this program. The present excellence and competitiveness of Louisiana's neurosciences will allow to attain the next level of accomplishments.

We envision an ongoing program after the FY 03, the preparatory phase of a five-year project. We have launched projects that will be the "proof of principle" that a neurobiotechnology/pharmaceutical infrastructure can be established in Louisiana. We are establishing preliminary core resource facilities within each institution, including recruitment and training of faculty and technicians, acquisition of key equipment, development of a strategic plan, and the implementation of pilot studies.

Economic Impact

- The basic knowledge that will be generated, and the enhanced capacity for multidisciplinary research, will have an immediate and beneficial impact upon the State's economic development in the following ways:
- The creation of start-up companies will be fostered. With retention of the patents within the State, the benefits of both profits and new employment opportunities for a newly created, highly educated work force will accrue to Louisiana.
- The consortium will become a magnet to attract existing pharmaceutical/ biotechnology companies or their subsidiaries to the State. These companies demand close proximity with the kind of expertise/research teams/ infrastructure that the consortium will nurture.
- The development of unique capabilities for brain imaging, along with comprehensive research efforts, will bring the proceeds of large-scale clinical trials to the participating academic institutions, thereby complementing and enhancing the public-funding investment.
- The discoveries in brain functioning and alleviation of the human costs of neurological diseases will improve quality of life for citizens nationally, and in particular, will be a unique opportunity and resource for sophisticated diagnostic procedures and new therapies for Louisiana citizens who may suffer from these debilitating diseases.

Program Director / Principal Investigators

Nicolas G. Bazan, M.D., Ph.D.



Boyd Professor, Ernest C. and Yvette C. Villere Professor of Ophthalmology, Biochemistry and Molecular Biology, Neurology Director, LSU Neuroscience Center of Excellence

- Director of the Louisiana State University Health Sciences Center Neuroscience Center of Excellence (New Orleans).
- Professor of Ophthalmology, Biochemistry and Molecular Biology, and Neurology.
- Yvette C and Ernest C Villere Endowed Chair for the Study of Retinal Degeneration and the Boyd Professorship, the highest academic honor in the LSU system.
- Molecular targeting in neuroprotection, synaptic signaling, pain and neurodegenerative diseases.

Richard Harlan, Ph.D. and James Zadina, Ph.D.



◀ Professor, Director of the Neuroscience Training Program

- Professor of Structural and Cellular Biology and Director, Neuroscience Program. Neuroendocrinology; gene expression in the brain; neuroanatomy of neuropeptides and protein kinase C isoforms; steroid hormone actions on the brain; addictive drugs; effects of morphine on the brain; brain development.

James Zadina, Ph.D., Professor of Medicine and Director of Neuroscience Laboratory, V. A. Medical Center ▶

- Discovery of two morphine-like chemicals in the brain, the endomorphins, has been cited over 385 times in the scientific literature. A goal of his current studies on the role of endomorphins and their analogs in pain and reward is to develop potent new analgesics with fewer side effects relative to current opioid medications.
- Dr. Zadina has published over 150 scientific papers. His research has been funded by competitive grants from the VA, NIH, ONR, PVA, and Louisiana Board of Regents.



Anil Nanda, M.D., FACS



Professor and Chairman of the Department of Neurosurgery at LSU Health Sciences Center in Shreveport

Appointed Chief of Neurosurgery in 1990 and then the first Neurosurgery Department Chairman with its establishment in 1995, Dr. Nanda has ushered the growth and development of University Neurosurgery through the vision he continues to share with the department's faculty and staff. In spring of 2002, Dr. Nanda was also successful in seeking accreditation of a neurosurgery residency program at LSUHSC in Shreveport, the first such residency program to be approved in the last five years.

Dr. Nanda is a member of the American Medical Association, the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, the Louisiana Neurological Society, the Louisiana State Medical Society, the Shreveport Medical Society and the Shreveport Surgical Society.

Pain and Opiates

Drs. James Zadina, Richard Harlan, Meredith Garcia, Brad Taylor, Bret Smith

- Nearly one third of the American population experiences chronic, often debilitating pain, costing society hundreds of billions of dollars per year in lost productivity and medications.
- Neuroscientists at Tulane have discovered and characterized peptides that are produced by the brain, and that can control certain forms of pain.
- The focus will be on determining whether these new pharmaceutical agents are appropriate and useful for treating pain in humans.

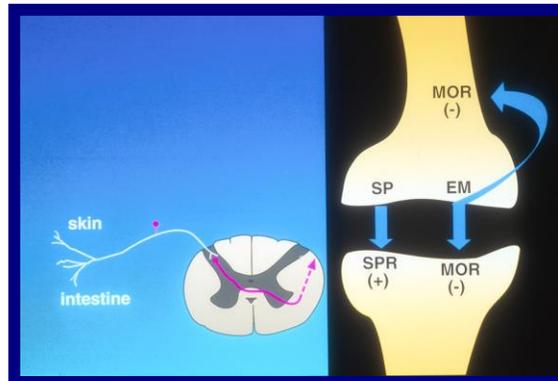
Current Therapies for Chronic Pain Often Rely on Opiates

- Opiates have addictive potential
- Vicodyn and other pain-controlling opiates have become major drugs of abuse
- Patients become tolerant to opiates, requiring larger doses to produce pain relief
- Opiates also depress breathing, sometimes to the point of coma or death

Potential of new pharmaceutical approaches to pain

- Endogenous peptides that control pain have been discovered by neuroscientists at Tulane, notably Dr. James Zadina
- These peptides, or closely-related peptides, can control pain at doses that do not produce breathing problems
- These peptides may also control pain without being addictive

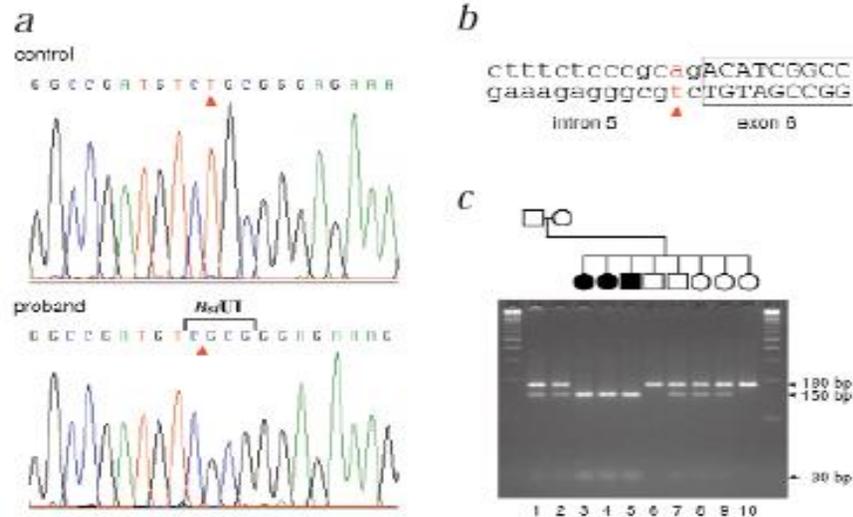
Pain, and a model of how endogenous peptides (endomorphins, EM) discovered at Tulane University help to control pain.



Deafness and Other Hearing Disorders

Drs. Meredith Garcia, Prescott Deininger, Ronald Amedee, Cassie Cusick

- Nearly 10% of Americans experience deafness or other hearing impairments
- Neuroscientists at Tulane and LSUHSC have identified two genes that are mutated in people with certain types of hearing loss.
- New strategies for delivery of pharmaceutical agents or gene therapy systems will be developed to treat or prevent hearing loss, especially among at-risk populations, such as the Acadians of southwest Louisiana.

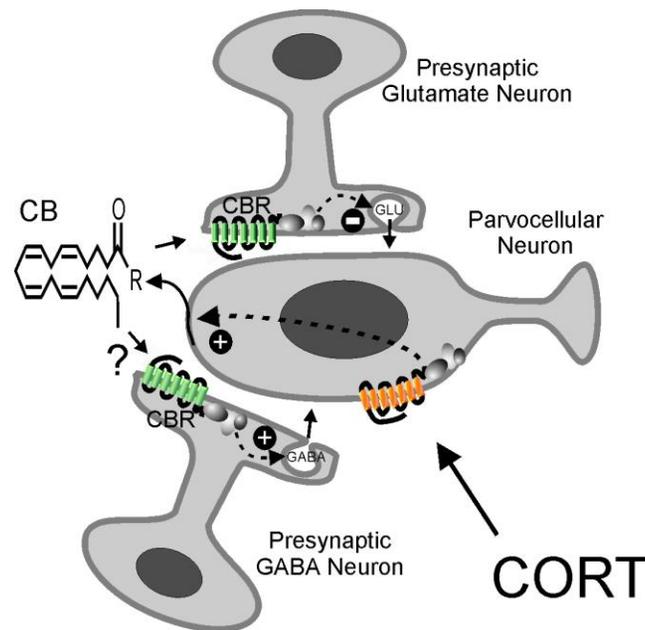


DNA sequence analysis of a Louisiana patient with a genetic mutation of a gene involved in hearing.

Stress And The Brain

Drs. Jeff Tasker, Carol Phelps, David Hurley, Gary Dohanich, Richard Harlan, Jennifer Vasterling

- Chronic stress can damage the brain and can lead to clinical depression, in part through altered secretion of stress hormones that act on the brain.
- Depression costs the nation more than \$30 billion per year.
- Tulane has a rich tradition in studies on the interaction between the brain and the hormone systems, stemming from the Nobel prizing winning work of Andrew Schally and his colleagues.
- Studies will focus on understanding the molecular events that occur in individual neurons in response to stress and to stress hormones, with the hope of developing new pharmaceutical agents to reduce the damaging effects of stress.
- Additional studies will focus on cognitive and learning deficits in people who have experienced trauma, including military veterans who experience post-traumatic stress disorder.



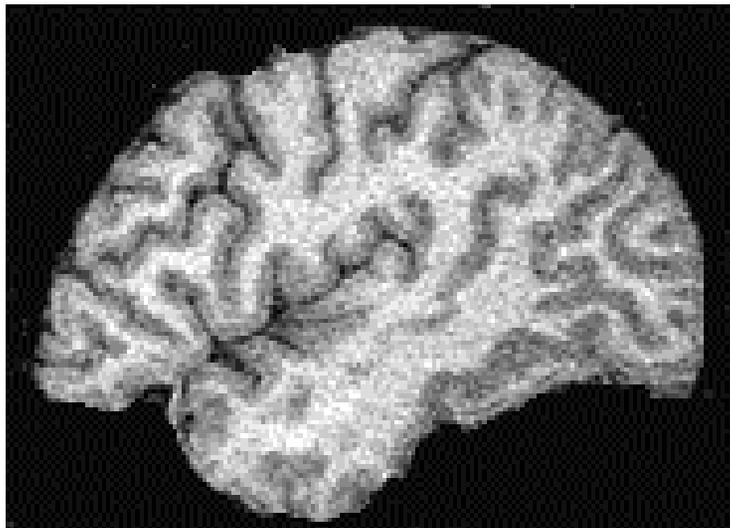
Model of how the stress hormone cortisol may affect neurons that are involved in the stress response.

Normal Development and Recovery Of Brain Function

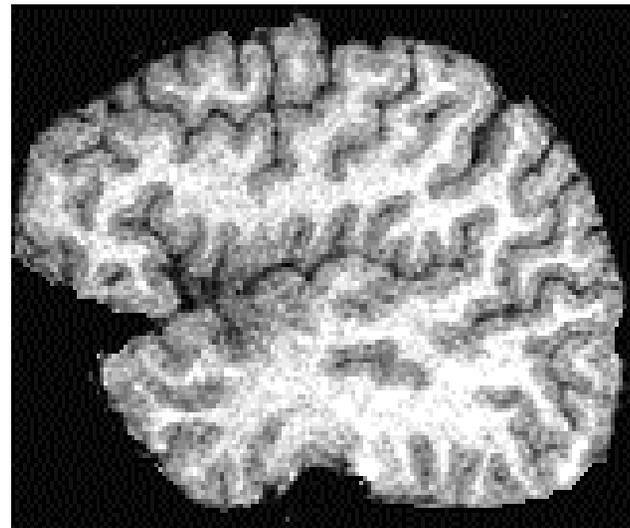
Drs. Anne Foundas, Jennifer Vasterling, Joe Dien, Catherine Cusick, Charles Zeanah, Michael Scherringa, Neal Boris, Leon Weisberg, Elizabeth Crabtree-Hartman, Dave Corey

- The previous concept that brain damage is irreversible has proven to be wrong.
- Neuroscientists at Tulane Health Science Center are using sophisticated imaging techniques to visualize normal brain development and brain damage and recovery of function after stroke, Alzheimer's disease and psychological trauma.
- The goal is to image the brain at the molecular level, in living people, to gain a greater understanding of the chemical imbalances that may occur with brain damage or developmental disorders.

Structural anomalies in a subject with stuttering.



Control Subject



Stutter Subject

Mechanisms of Pain and Inflammation

Drs. Jian-Guo Cui, Chu Chen, Walter Lukiw, Pranab Mukherjee, Heather Scuderi, Anthony Vaccarino

Objective

To develop new applications in the area of pain and inflammation of a family of low-molecular weight compounds invented by Dr Nicolas Bazan and collaborators. (Patent filed: "Novel 5-lipoxygenase Inhibitors: (2-Azinylamino) Quinone Derivatives")

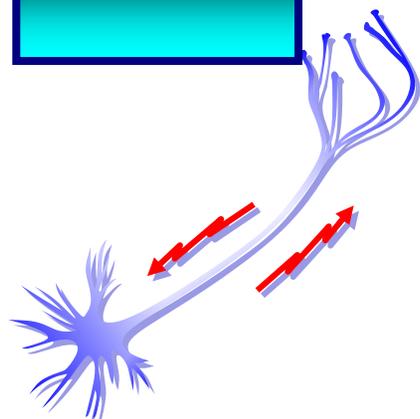
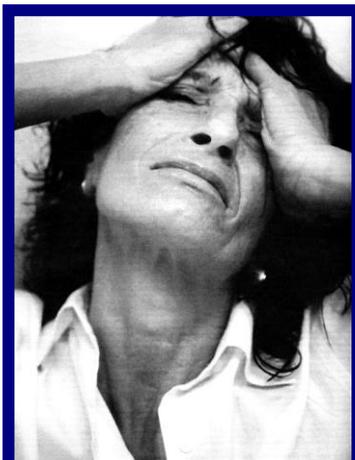
The Challenge

Over-the-Counter
Headache

Tylenol and other pain relievers may sometimes cause what they're meant to cure.

New York Times
Jan. 12, 2003

Pain Therapeutics
A New Era of Research, Innovations,
and Commercial Opportunities



Meeting The Challenge

Using various behavioral paradigms we will examine the role of 5-lipoxygenase pathway and PAF in mediating inflammation, inflammation-related pain, and neuropathic pain syndromes.

The identification of critical steps of diseases coupled with drug discovery leads to inventions and research translation. The retention of this know-how in Louisiana fosters the creation and development of pharmaceutical/biotechnology companies.

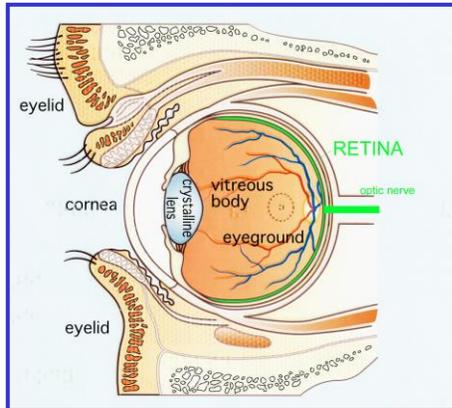
During inflammation, platelet-activating factor (PAF) and arachidonic acid (AA) are released from cell membranes. AA can be converted by cyclooxygenase-2 (COX-2) into prostaglandins, or by lipoxygenase-2, we have identified the involvement of lipid mediators in the mechanisms of pain and inflammation. We have discovered a promising family of low-molecular-weight compounds, inhibitors of 5-lipoxygenase, as potential anti-inflammatory drugs (Bazan, patent pending). The present work will assess whether or not these compounds are also analgesics.

Investigations in Dr. Bazan's laboratory have resulted in the discovery of several compound inhibitors of 5-LO activity and with minimal or no effect on cyclooxygenase-1 and -2 (COX-1 and COX-2) activity.

The receptor for platelet-activating factor (PAF-R) is a key component of signaling between pain and inflammation. We have available for our use mice that are deficient in the gene potentiation in hippocampus, where PAF-R activity is critical.

Age-related Macular Degeneration and Other Retinal Degeneration Diseases

Drs. William Gordon, Sebastian Barreiro, Soledad Cortina, Victor Marcheselli, Pranab Mukherjee, Helene Varoqui



Normal Glaucoma Macular Degeneration

Objectives

- Our goal is to understand to identify new transporter genes involved in glutamatergic neurotransmission in the retina.

Making A Difference

- Our research allows further understanding of the mechanism by which blinding eye diseases develop and possible avenues for treatment.
- Identification and characterization of key players at the gene and protein levels will allow development of target specific drugs.
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Meeting The Challenge

To gain an understanding of the mechanisms of photoreceptor death and survival. This project will explore both rods and cones; however, the aim is to define the usefulness of the rat to study cone photoreceptors. This information will provide new experimental approaches to develop pharmacologic targets and therapies to promote cone photoreceptor survival in central retinal blinding eye diseases, such as macular degeneration.

We envision the creation of platform technologies for the development of new companies performing research in the area of retinal diseases and ophthalmology.

We recently identified a novel mechanism by which DNA repair is activated *before* photoreceptor death. Identification of this mechanism by which mechanism raises the possibility of designing new drugs to rescue the photoreceptors that die in patients with age-related macular degeneration and retinitis pigmentosa. In the experimental model that we used, we are also able to distinguish between the loss of *rod photoreceptors* and *cone photoreceptors* - in the human macula, there are mostly cone photoreceptors.

Disease Targets

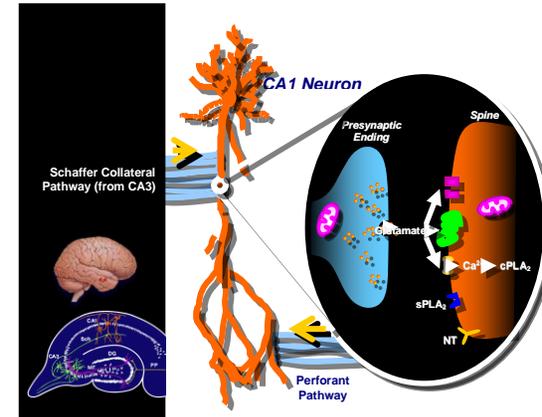
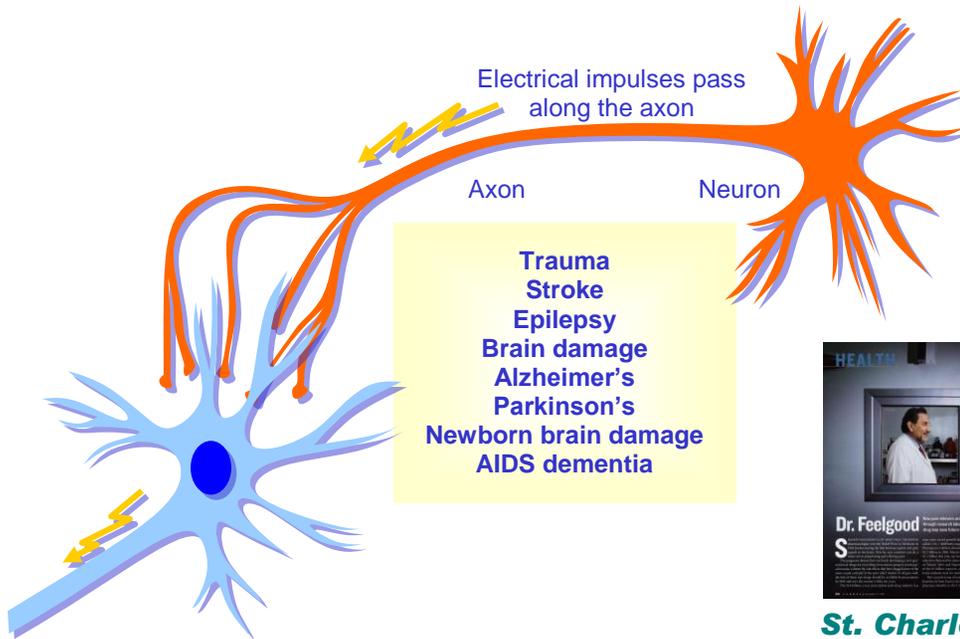
- Retinitis Pigmentosa
- Age-related Macular Degeneration
- Glaucoma
- Diabetic Retinopathy

Synaptic Signaling And Neuroprotection

Drs. Nicolas G. Bazan, Chu Chen, Victor Marcheselli, Alberto Musto, James Moisés, Xiao Hua Tian

Objectives

Our goal is to better understand synaptic signaling and to develop novel strategies for neuroprotection.



Economic Development Impact

These projects provide a foundation of original research that stimulates other external funding possibilities, such as from the National Institutes of Health. Industrial partners include the local biotech company, St. Charles Pharmaceuticals.

Anticipated Benefits

- Currently there are no cures.
- Future effective treatments and possible cures for these diseases will result in a more productive and healthy childhood and adult population in Louisiana and the nation.



St. Charles Pharmaceuticals

Meeting The Challenge

To develop new applications of compounds presently patented by Dr. Nicolas Bazan and collaborators for use in the areas of traumatic brain injury, Alzheimer's disease, and stroke. To identify cellular and molecular mechanisms of neural injury and neuroprotection in traumatic brain injury, Alzheimer's disease, and stroke.

Traumatic Brain Injury

Use of models allows us to study the events triggered by trauma and to explore reparative strategies or drugs with neuroprotective potential. These models produce transient intracranial pressure increases, reduction of pressure autoregulation (leading to a late increase of intracranial pressure), and edema, possibly having vasogenic origin.

Alzheimer's Disease

We hypothesize that inflammatory processes accompany normal brain aging, however these are greatly amplified in Alzheimer's brain disease.

Stroke

Examination of the complex cascade of lipid-signaling events in hippocampus, cultured hippocampal neurons, with the goal of filling in the gaps in knowledge of the significance of intraneuronal signaling that modulates gene expression

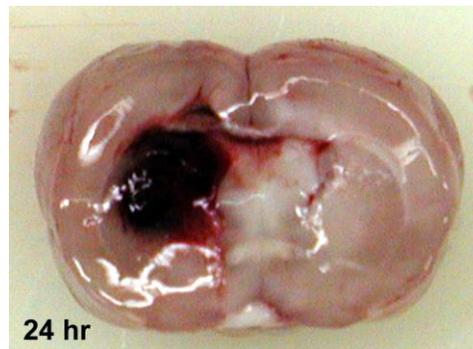
Mechanisms of Brain Injury After Hemorrhagic Stroke

Drs. John Zhang, Anil Nanda, Steve Alexander, feng Xiao, Neil Granger, Ronald Korthuis, Matthew Grisham, Tak Yee Aw

- Hemorrhagic stroke is responsible for more than 50% of stroke-related deaths.
- Neuroscientists at LSU Health Sciences Center in Shreveport are working to define underlying mechanisms of brain injury and dysfunction, test potential therapeutic strategies, and foster translational research on hemorrhagic stroke.
- The specific aim is to investigate the mechanisms responsible for the early brain injury that occurs after hemorrhagic stroke.
- Studies will focus on models of hemorrhage with brain infarction, rupture of the blood-brain barrier, brain edema, neurological dysfunction, and mortality established using histology, immunocytochemistry, and neurological techniques.

INITIAL HYPOTHESIS:

Activation of Mitrogen-Activated Protein Kinase (MAPK) and Matrix Metalloproteinase (MMP) pathways is involved in the early stage of brain injury after hemorrhagic stroke.



This is a coronal section subjected to experimental ICH produced by injection of 100 µl of autologous blood.

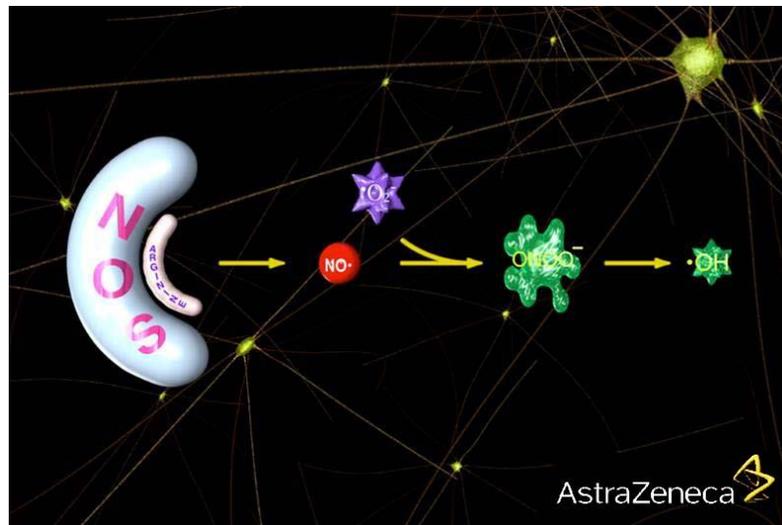
Mechanisms of Oxidative Damage and Neuro-Protection

Drs. John Zhang, Tak Yee Aw, Matthew Grisham, Lynn Harrison, Pedram Ghafourifar, Matin Feelisch, Neil Granger, Sandra Roerig, Adrian Dunn, Roger Kelley, Richard Zweig, Arthur Freeman, James Patterson

- Neurodegeneration occurs for a variety of reasons, many of which are unknown.
- Molecular mechanisms of neurodegenerative damage frequently follow specific patterns, may involve oxidative damage, excess excitation by amino acid neurotransmitters, such as glutamate, and mechanisms that mimic apoptosis.
- The expression of specific genes, such as NFkB and IFkB is also common.
- Researchers at LSU Health Sciences Center in Shreveport have secured substantial funding to study such mechanisms.

SPECIFIC AIM:

Focus on NO (nitric oxide) and its synthesis, and in particular the role of inducible NOS (iNOS), for example, in inflammation in the vasculature and in the brain associated with neurodegenerative disease, and in the production of abnormal pain.



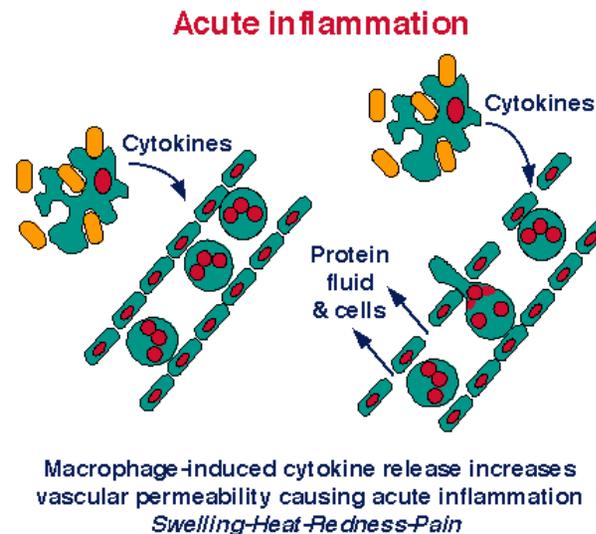
Role of Cytokines In Cell Damage And Neuropsychiatric Abnormalities

Drs. Andrew Dentino, Patrick Wood, David Scarborough

- Cytokines can act as messengers between the immune system and the brain.
- There is an important balance between the physiological stress systems and cytokines.
- Multiple cytokines are known to be produced during responses to infections and tissue damage, and following brain injury, for example after a stroke.
- Researchers at LSU Health Sciences Center in Shreveport are investigating the role of cytokines in depression and other neuropsychiatric problems in the elderly, as well as the role of cytokines in chronic pain and the endocrine effects of cytokines.

SPECIFIC AIM:

To establish that cytokine production and/or increased circulating concentrations of certain cytokines are responsible for the induction of neuropsychiatric symptoms in patients with stroke damage and/or neurodegeneration.



Program Director Nicolas Bazan — Neurobiotechnology Initiative 2002

TULANE UNIVERSITY - P.I. Richard Harlan

LSUHSC-NO - P.I. Nicolas Bazan

LSUHSC-S - P.I. Anil Nanda

