DIRECTORY OF GRANT AWARDS
2007 GRANT CYCLE

NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

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JUNE 2007

NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

This data was compiled in compliance with the New Jersey Commission on Brain Injury Research's statutory mandate, N.J.S.A. 52:9EE-1, "….to compile a directory of brain injury research being conducted in the State."

The information contained within this directory is not all-inclusive. The research projects and researchers listed in this directory are all based in the State of New Jersey and have applied to and received funding during the fiscal year 2007 grant cycle. The research projects are not categorized, or listed in any particular order.

This directory is not a complete listing of all scientific research being performed within the State of New Jersey due to the proprietary nature of the research being conducted at various institutions throughout the State. In addition, institutions are not obligated to share their research information with the New Jersey Commission on Brain Injury Research.

Please feel free to contact the New Jersey Commission on Brain Injury Research at P.O. Box 360, 369 S. Warren Street, Trenton, New Jersey, 08625. The Commission's office can be reached by telephone at 609-633-6465, by fax at 609-943-4213, or by e-mail at NJCBIR@doh.state.nj.us.

For information on the New Jersey Commission on Brain Injury Research's grant award process, grant applications and deadlines, please see: www.state.nj.us/health/njcbir.

2007 MEMBERSHIP INFORMATION

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

John E. Pintar, Ph.D. – Principal Investigator
University of Medicine & Dentistry of New Jersey - Robert Wood Johnson Medical School
Grant Award: $300,000

Proposal Title: *Role of IGF Binding Proteins in Response to Brain Injury*

Traumatic brain injury leads to multiple changes in gene expression by cells within and surrounding the injured tissue, although the functional significance of most of these changes remains poorly understood. There is strong evidence indicating that the peptide "insulin-like growth factor I" (IGF-1) can both be neuroprotective and perhaps also stimulate cell division of stem cells that could replenish injured neural tissue. Thus it is important to understand how IGF activity is regulated. One set of proteins that regulate the activity of IGF-I is the insulin-like growth factor binding protein (IGFBP) family, which is up-regulated in several models of brain injury.

We propose to determine the functional role of these IGF binding proteins by determining whether alterations from the normal response to TBI occur in mutant strains of mice already produced in our laboratory that lack these proteins. We will perform two types of TBI in wild-type and mutant mice and then compare the extent of apoptosis, glial and neuronal responses, and stem/progenitor cell proliferation and differentiation between wild-type and mutant mice. Completing these studies will reveal specific processes dependent on binding protein function. Thus the proposed experiments will provide functional insight into the roles of the insulin-like growth factor system in neural maintenance and restoration and potentially lead to more efficacious treatments for TBI.

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Patrizia Casaccia-Bonnefil, M.D., Ph.D. – Principal Investigator
University of Medicine & Dentistry of New Jersey - Robert Wood Johnson Medical School
Grant Award: $300,000

Proposal Title: *Molecular Mechanisms of Delayed Axonal Damage in Traumatic Brain Injury*

A slow process of death and breakage of nerve cells continues to silently occur for months and years after the original injury in at least 225,000 patients nationwide and 12,000 patient in the State of New Jersey every year. Although this progressive damage cannot be easily detected by the conventional imaging methods, its clinical manifestations are a common finding and may range, depending on the severity of the disease, from altered personality traits and memory loss to dramatic deterioration of the clinical signs. Despite the enormous emotional and financial burden that this disability may have on the patient's family, still very little is known about the signaling events responsible for this "silent" damage that continues to accumulate in the neural cells of patients with traumatic brain injury. Thus, no therapy is available for the prevention of these delayed clinical manifestations and this contributes to the increasing financial costs for the general public, due to the debilitating nature of the symptoms in young adults.

This experimental plan is aimed at defining the mechanisms responsible for the silent and persistent killing of nerve cells that occur for a long time after the original accident. Preliminary data obtained from our laboratory and from our collaborators at the Center for Brain Injury and Repair at U Penn, suggest a possible cause for the damage to neural cells occurring months after the injury. Therefore, we have designed a multidisciplinary experimental plan to test this possibility. It is anticipated that the results of the proposed experiments will enhance our knowledge on the causes of the delayed damage to brain cells and may lead to a breakthrough in understanding the mechanisms responsible for the late and progressive clinical symptoms. The long term goal is to continue these studies towards the development of novel therapies to chronically administer to patients with TBI in order to prevent long-term memory loss, behavioral changes and neurological disability discovery of the mechanisms responsible for the long term neurological disabilities.

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Christopher Rongo, Ph.D. – Principal Investigator
Rutgers, The State University of New Jersey – Waksman Institute
Grant Award: $299,024

Proposal Title: *Genetic Analysis of Excitotoxic Neuronal Death*

Brain injury from trauma or ischemia (oxygen deprivation) can result in the loss of mobility, sensation, memory, cognition, and autonomic function. The initial events are restricted to a small region of the brain; however, damaged neurons release large quantities of the neurotransmitter glutamate into surrounding brain tissue. High levels of glutamate overactivate glutamate receptors present on surrounding neurons, resulting in calcium influx and subsequent cell death (excitotoxicity). These dying neurons release their own stores of glutamate, leading to yet more glutamate accumulation and waves of dying neurons spreading out from the injury site. We aim to study excitotoxicity using a genetic approach in the nematode C. elegans, which uses glutamate receptors in sensory circuits that are strikingly similar to the circuits found in the human brain. My lab studies genes that regulate these receptors.

The overactivation of these same receptors in C. elegans leads to excitotoxic neural death, and provide an excellent model system with which to study the process of neuronal injury. Preliminary results suggest that mutations in genes that regulate glutamate signaling or intracellular calcium levels can block neuronal degeneration. This affords us an easy and inexpensive method (forward genetic screening) for identifying other genes involved in this cell death process, and funding of this proposal would allow my lab to expand into the field of glutamate-mediated excitotoxicity and brain injury using C. elegans as a model.

This proposal satisfies the goals of the NJCBIR in two ways. First, we will provide insight into the mechanism of excitotoxic death and identify agents that block glutamate receptor activation (or otherwise restore calcium levels within neurons), which can help limit damage after brain injury. Second, we will identify factors that regulate glutamate receptor function; these factors can be targeted to help to strengthen synapses, thereby improving brain function after injury. Researchers have previously used C. elegans to understand apoptotic cell death in humans; indeed, the Nobel Prize in Physiology and Medicine for 2002 celebrated these achievements. My lab has so far discovered 14 genes that regulate glutamate receptors; all 14 have human equivalent genes playing a similar or identical role in humans and C. elegans, suggesting that our findings in C. elegans are likely to be applicable to human health.

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Haesun A. Kim, Ph.D. - Principal Investigator
Rutgers, The State University of New Jersey – Biological Sciences
Grant Award: $299,999

Proposal Title: *Effect of Diffuse Axonal Injury on Dendrite and Myelin*

After a closed head injury, the shifting and rotation of the brain inside the skull causes a shearing injury to the brain's complex circuitry. This axonal shearing can occur in localized areas or throughout the brain. The latter is called "diffuse axonal shear" or "diffuse axonal injury (DAI)". The brain cells that are particularly important to learning and memory are apparently more vulnerable to DAI.

Dendrites and myelin are important structural components of neurons in our brain. Dendrites, short axonal projections growing out from a neuron, are important for connecting individual neurons, as they enable establishing communication among a group of neurons. Several studies have shown that cognitive dysfunction (a common feature of brain injury patients) is associated with altered dendritic morphology. The first aim of the proposed study is to determine the effect of DAI on altering dendritic morphology and its function.

Majority of our brain is composed of axons that are myelinated. A myelin sheath insulates these individual axons and is crucial to the speed and accuracy of its electrochemical impulse. If the myelin sheath is structurally damaged, then its electrophysiological properties are disrupted, and the electrochemical impulse will become abnormal and uncoordinated. Therefore, preventing further damage to myelin and facilitating re-myelination of the injured axons are keys to achieving functional recovery in patients with brain injury. The second aim of the study is to determine the effect of DAI on myelin and how myelin affects the axonal response to injury.

For the study, we will use an innovative neuronal culture system in which DAI effect on axons can be re-produced in laboratory. This system will be combined with "myelinated neuronal culture" to induce DAI in myelinated axons. Altogether, our combined culture system will allow us to study the effect of DAI on both dendrites and myelin.

In summary, our proposed studies aim to increase insight into understanding dendrite and myelin injury after brain injury and its effect on neuron function. This is important and may lead to development of novel strategies to help devise treatment for preventing disability and promote recovery of the damaged neurons in patients with brain injury.

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Bryan J. Pfister, Ph.D. - Principal Investigator
New Jersey Institute of Technology
Grant Award: $144,578

Proposal Title: *High Throughput Axon Injury System for the Study of Brain Injury Mechanisms*

Every fifteen seconds someone suffers a traumatic brain injury (TBI). The predominate pathology in head trauma is diffuse, traumatic injury to axons (nerve fibers) throughout the brain and is believed to be a major factor in patient outcome. Traumatic axonal injury is thought to occur due to a rapid stretching of axons as a result of damaging head motions that can occur in motor vehicle crashes, falls, and assaults. Traumatic axonal pathology is microscopic and there are currently no biomarkers for detecting damaged axons in living human or animal models. A definitive diagnosis can only be obtained histopathologically in post-mortem studies. Several in vitro models have been developed to study the real-time progression of TBI. Only one model, however, uses a rapid stretch to injure isolated axons, directly mimicking the mechanical deformations that occur in TBI.

This powerful model has contributed to the discovery of key biological mechanisms of traumatic axonal injury. Unfortunately, this model is only utilized by two collaborating laboratories at the University of Pennsylvania. While it is a clinically relevant model, it is difficult to use, and its low experimental yield has prevented important and well founded investigations where high throughput methods are required (such as treatment screening).

As a result, pharmaceutical and neuroscience research environments often view TBI research as an expensive and low-yield effort that can only be accomplished through animal models. The discovery of new treatments for many diseases, however, is accelerated with the use of high throughput tissue culture techniques. They are more cost effective and rapid than animal models, providing an efficient method for screening for biomarkers and potential therapies. Accordingly, the next big step for in vitro TBI models is to provide the similar efficiency and throughput the multi-well plate brought to tissue culture experimentation. The purpose of this proposal is to create a multi-well high throughput neural injury device to accelerate the study of TBI mechanisms. This system will have the capability to rapidly screen for biomarkers and potential interventions, study mechanisms of therapeutics, and generate large tissue samples necessary for proteomic and genomic analyses. For easy implementation in any laboratory, this system will be automatic and not require a high level of expertise to operate.

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