DIRECTORY OF GRANT AWARDS
2012 GRANT CYCLE

NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

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JUNE 2012

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 2012 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.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

Helen Genova, Ph.D.
Kessler Foundation
Grant Award: $462,103

Project Title: *The Longitudinal Examination of the Relationship Between White Matter Pathology & Cognitive Impairment in Traumatic Brain Injury using Diffusion Tensor Imaging*

The current proposal will examine the relationship between reduced white matter integrity, assessed by Diffusion Tensor Imaging, and cognitive decline in chronic TBI. 5.3 million people in the United States experience long-term disability due to a Traumatic Brain Injury (TBI). While some individuals may recover cognitively from TBI, many individuals experience long-term cognitive impairment which can negatively impact quality of life and the ability to maintain relationships and careers. An understanding of why some individuals with TBI show improved cognitive outcome, while others decline is critical to the prescription of early interventions, such as cognitive rehabilitation. However, researchers have consistently failed to find appropriate predictors of cognitive outcome. Pathology assessed by conventional MRI following TBI does not appear to be strongly associated with cognitive measures, mainly due to the fact that traditional MRI methods cannot detect microscopic damage.

A newly emerging neuroimaging technique, Diffusion Tensor Imaging (DTI) has been shown to be sensitive to microscopic damage, such as Diffuse Axonal Injury (DAI) and damage to white matter, which is strongly correlated with cognitive impairment following TBI. However, no one to our knowledge has examined the relationship between changes in white matter integrity over time (using DTI) and changes in cognition over time in a chronic sample of TBI (more than 2 years post-injury).

The goal of the proposed study is to examine changes in both white matter integrity and cognition over time and assess their relationship with one another. Additionally, the predictive value of DTI will be investigated by examining white matter integrity at time point 1 and determining if it predicts cognitive impairment at time point 2. If DTI proves to be a useful biomarker of cognition in TBI, it will have critical value to both scientists and clinicians to determine which individuals should be targeted for specific interventions to improve white matter integrity. Further, targeting of "at risk" individuals will enable us to utilize interventions aimed at halting cognitive decline.

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Martin Yarmush, Ph.D.
Department of Biomedical Engineering
Rutgers, The State University of NJ
Grant Award: $540,000

Project Title: *Evaluation of Encapsulated Mesenchymal Stromal Cells as a Therapeutic for Traumatic Brain Injury Treatment*

Traumatic brain injury (TBI) begins with mechanical disruption of tissue, which triggers a cascade of secondary insults that injures neurons for weeks, and even months, following the initial trauma.

Many of the devastating, long-term functional consequences of TBI may be avoided by therapies that target secondary inflammatory effects. Although current anti-inflammatory treatment approaches have been only minimally effective, an expanding body of evidence suggests that transplanted Mesenchymal Stromal Cells (MSC) can improve functional traumatic nervous system outcomes via secretion of cytokines and neurotrophic factors. However, current MSC infusion strategies are inefficient and lack the necessary control features needed for clinical translation.

Therefore, one of the objectives of our proposed studies is improve upon current TBI therapeutics by determining whether the anti-inflammatory and neurotrophic benefits of MSC can be harnessed and optimized by encapsulating MSC within an alginate matrix. The encapsulation approach allows the MSC to sense soluble factors in the environment without directly interacting with tissue. We have shown that this strategy improves the anti-inflammatory capabilities of MSC, and that this approach improves outcomes after spinal cord injury. However, we have yet to test the system in models of brain injury. As such, this research meets the funding priorities of the NJCBIR, specifically the study of strategies to promote neuronal growth and survival, and improve brain function after injury; and the evaluation of the efficacy of interventions that prevent or reduce secondary injury.

Additionally, this research is a collaboration between two scientists, Dr. Shreiber from Rutgers, who specializes in spinal cord injury biomechanics and regeneration, and Dr. Yarmush who has a wealth of experience in evaluating MSC encapsulation and therapeutic approaches in a number of injury models.

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MULTI-INVESTIGATOR RESEARCH GRANT RECIPIENT:

Gabriella D'Arcangelo, Ph.D.
Department of Cell Biology & Neuroscience
Rutgers, The State University of NJ
Grant Award: $2,034,000

Overall Project Title: *The Role of mTOR Signaling in Recovery after Traumatic Brain Injury*

This project investigates the role of Akt/mTOR signaling in recovery after traumatic brain injury and other types of neuronal injury. Traumatic brain injury (TBI) is no longer a silent epidemic. On track to become the third leading cause of death and disability worldwide by 2020, the recent public awareness surrounding TBI only increases the need to find an effective treatment for this disease.

In this proposal, we study one central signaling pathway (mTOR/Akt) as a possible approach for developing new treatment approaches for TBI. This specific signaling pathway may be important in repairing the brain after TBI because it plays a significant part in shaping the function of neural circuits. We evaluate if this signaling pathway is activated in both in vivo and in vitro models of TBI, test if controlling parts of this pathway will improve recovery in the wiring and function of neural circuits after injury, and examine if controlling this pathway with drug treatment will improve outcome in a preclinical model of TBI. Our ambitious scope is made possible through the coordinated activities of investigators across three distinct projects, and will provide a strong foundation that can progress into federal support beyond the timetable of the proposed research plan.

Sub-Project #1 Title: *Analysis of the Akt/mTOR Signaling Pathway after Pten Deletion, Traumatic Brain Injury or Neuronal Injury*

Gabriella D'Arcangelo, Ph.D., Department of Cell Biology & Neuroscience, Rutgers University

In this project, we will generate genetically modified mouse lines in which the Akt/mTOR signaling pathway is upregulated in distinct neuronal populations, and determine whether in vivo TBI or in vitro neuronal injury modulates this pathway. We examine the progression of Akt/mTOR activation over time following injury. Biochemical assays measure the levels of signaling activity, and confocal fluorescence microscopy techniques identify cell types in which these events take place. Our major hypotheses are that Akt/mTOR activation alters neuronal growth, differentiation and function in Pten mutant mice, and that this signaling pathway also occurs in response to TBI/mechanical injury. Here we determine if the activation persists for a prolonged period of time after injury, and if it is influenced by the severity of the injury.

Sub-Project #2 Title:
Effects of PTEN Loss on Functional Recovery after Traumatic Brain Injury

Bonnie Firestein, Ph.D., Department of Cell Biology & Neuroscience, Rutgers University

This study utilizes a genetic approach to examine the effect of mTOR activation by PTEN deletion after TBI using both in vivo and in vitro models. With a systematic analysis of the mTOR activation pathway after mechanical trauma in vitro and in vivo (Sub-Project 1) and a goal of testing therapeutic options in this pathway in vivo (Sub- Project 3), this project uses

genetic tools from Subproject 1 to test how the mTOR pathway contributes to the structure and function of neural circuits after mechanical injury. We test the general hypothesis that neuronal damage and loss of functionality is decreased when PTEN is deleted, and as a result, mTOR activity is increased. Imaging, electrophysiological, and neurobehavioral assays will be used to compare recovery in normal and mutant mice and cultures from these mice.

Sub-Project #3 Title: *Role of mTOR in Recovery from Traumatic Brain Injury*

David F. Meaney, Ph.D., Department Chair, Department of Bioengineering, University of Pennsylvania, Philadelphia, PA

This project uses pharmacological approaches to modulate the activity of mTOR in vivo and in vitro, examining the consequence of these manipulations on recovery from TBI. Our general hypothesis is twofold: (a) mild mechanical injury leads to an enhancement in mTOR activation that causes an increase in neural network function without a change in dendritic morphology, and (b) more severe mechanical injury will trigger an increase in mTOR activation that causes a change in dendritic morphology, an impairment in network function, and a vulnerability to secondary chemical injury. We test the possible neuroprotective role of mTOR/Akt activation/inhibition on neuronal survival and improvement in neural circuit function and neurobehavior, and we examine if the role of mTOR/Akt changes across the severity of TBI.

Our major hypotheses include: Mechanical injury activates mTOR/Akt across the injury severity spectrum in vivo and in vitro. Mild mechanical injury leads to an enhanced network activity, sustained at least in part by mTORC1 assembly. Moderate mechanical injury in vitro and in vivo leads to a change in dendritic morphology that reduces the functional connectivity of local microcircuits. Alterations in dendritic morphology are mediated by the neuronal cytoskeleton, and can be influenced by mTORC2. Protecting against this loss in the physical wiring of neural microcircuits mediated by mTOR/Akt triggered cytoskeletal reorganization - will help promote the recovery of neural circuits after traumatic injury.

To test these hypotheses, we use information on the timing and activation of specific mTOR/Akt pathway components after mild and moderate TBI in vivo (Sub-Project #1) to plan our pharmacological approaches. In addition, we integrate our studies with Subproject #2 that concentrates on how TBI in causes dendritic varicosities and circuit malfunction both in vitro and in vivo. Based on these data, we test if these morphological changes are influenced through the mTOR/Akt pathway.

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FELLOWSHIP RESEARCH GRANT RECIPIENTS:

Nolan Skop
UMDNJ - Department of Neuroscience
Grant Award: $86,700

Project Title: *Delivery of Neural Stem Cells Using a Multifunctional Microsphere Scaffold for Traumatic Brain Injury Repair*

This project aims at regenerating the brain after severe injury using neural stem cells transplanted within a novel, multifunctional tissue engineered scaffold.

Traumatic brain injury (TBI) affects approximately 1.7 million Americans each year. Injuries in people over the age of 65 years can be attributed largely to falls, whereas hits to the head, motor vehicle accidents or casualties of war are often the reasons for TBI in younger adults and children. Immediate consequences may affect cognitive or motor functions including the loss of mobility, coordination, memory, reasoning, sensations, emotions, ability to communicate and process information. Other effects may take a while to appear such as an increased risk for developing epilepsy, Alzheimer's disease, Parkinson's disease, or other neurological disorders. Medical expenses from hospital bills and rehabilitation services can exacerbate the problem, costing a person with TBI up to four million dollars in a lifetime.

Usually after a person sustains an injury the medical team will do what is necessary to minimize secondary damage to the brain as a result of the inflammatory response. Doctors try to maximize blood flow (which allows for oxygen and nutrients to supply the brain) while minimizing the swelling caused by intracranial pressure that may damage more cells. The central nervous system does not have the same regenerative capability as other organs of the body and there are currently no approved strategies to regenerate brain cells after TBI.

Stem cells have emerged for their therapeutic potential as an attractive cell source for neural regeneration. Despite significant progress in stem cell transplantation after brain injury, success has been limited. Cells are being transplanted into a lesion lacking a substrate and necessary nutrients to promote their growth and survival. We have created a novel biomaterial scaffold to be used with stem cells to promote neural regeneration after severe brain injury. In this application we are requesting funds to take our studies out of the tissue culture dish into an animal model of TBI to see whether by combining our scaffold with neural stem cells that new neurons and glial cells can be produced to heal the injured cerebral cortex.

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Starla Weaver, Ph.D.
Kessler Foundation
Grant Award: $199,764

Project Title: *The Effects of Task Switching Training on Traumatic Brain Injury*

The proposed research will use a task switching training to improve executive functioning and examine the neuroplasticity in patients with TBI.

More than three million Americans are estimated to be living with a lifelong disability as a result of TBI. Rehabilitation programs that are able to target and improve executive functioning are critical to reducing disability among patients. Task switching ability has been found to be the best predictor of performance on real-world abilities necessary for independent living. In task switching subjects switch between the performance of two simple tasks. A number of studies have demonstrated the potential for task switching training to improve performance, particularly among populations who show impairments in executive function.

The proposed research will use task switching training to improving executive function among patients with TBI. An initial behavioral experiment will be used to compare the effects of tasks switching training on patients with TBI, with the effects of task switching training on healthy controls, and the effect of a non-task switching, single task training on patients with TBI. A second experiment will examine the neural correlates of improvements in executive function that result from task switching training. fMRI will be used to compare activation patterns of TBI patients with poor or good outcomes following task switching training. Task switching training is hypothesized to lead to generalizable improvements of executive function that result in lasting benefits for patients with TBI.

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Andrea Giovannucci, Ph.D.
Princeton University
Department of Molecular Biology
Grant Award: $225,936

Project Title: *Optical Imaging and Computational Modeling of Cerebellar Injury*

This project will use optical functional imaging data from cerebellar circuitry to computationally model lost function and possible interventions.

Traumatic brain injury represents an enormous challenge for rehabilitation. Most therapies for TBI focus on the cerebral cortex (a.k.a. neocortex), which is a prominent site of injury. Less appreciated is the role of the cerebellum, the second-largest major division of the brain. The cerebellum and neocortex are heavily interconnected and are likely to play a tandem role in motor, social, and cognitive function. Brain circuits can change as a result of both injury and experience over time. This carries two implications for injury and rehabilitation. First, TBI can have long-term consequences in any brain structure that is connected to the site of injury. Second, neuroprosthetic interventions are potentially effective at sites that are distant to the site of injury.

This proposal takes two novel approaches to addressing long-term consequences of TBI using modern optical methods for observing and influencing brain activity. The first approach is two-photon microscopy, an advanced imaging method that allows brain circuits to be monitored for up to weeks. Two-photon microscopy will be used to monitor the consequences of TBI for cerebellar function. The second approach is computational simulation: we will adopt an understand-and-repair strategy, which can drive the design of therapeutic interventions at the cellular level. Our studies will provide a proof of concept for the rehabilitation of brain function by next-generation neuroprosthetic.

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PILOT RESEARCH GRANT RECIPIENT:

Sridhar S. Kannurpatti, Ph.D.
UMDNJ - NJ Medical School
Grant Award: $180,000

Project Title: *Mitochondrial Function and Translational Markers of Reorganization in Traumatic Bain Injury*

Functional Magnetic Resonance Imaging (fMRI) markers specific to mitochondrial function after traumatic brain injury will be developed to bridge existing gap in drug evaluation for brain injury. Humans sustain mild traumatic brain injuries under various circumstances. In survivors progressive deterioration in brain function occurs months to years after sustaining the injury. Structural markers of concussive injuries are not easily visible in anatomical clinical imaging rendering the visualization of brain lesions and subsequent healing after therapy difficult.

Functional Magnetic Resonance Imaging (fMRI) has emerged as an effective tool to study human brain function. Though expensive, it is a very powerful tool to image the brain without injecting any medication or invading the patient's body. Further, this does not involve any harmful radiation that the patient may be exposed to with other radiological imaging techniques such as PET, CT or X-ray. Due to its high speed in collecting images of the brain (several in a few seconds) they can be mathematically processed to visualize activity within the brain. Brain circuits alter after TBI with notable changes in neuronal cells and blood vessels that support them. One of the main causes for deficient brain function after TBI is impaired mitochondrial function. Mitochondria being the energy source of cells support several brain functions including the regulation of its blood supply and functioning of its neurons. When mitochondrial function is impaired after TBI, profound deficiencies occur in neurons and their supporting blood vessels. We hypothesize that this leads to altered activation of neural circuits leading to cognitive deficiency, sensory and motor dysfunction. This study will introduce innovative fMRI methods to map brain function after TBI to track the brain reorganization after treatment with mitochondria altering drugs.

This proposal will characterize the workings of normal and injured mitochondria in the intact animal without any simplification and decipher its relationship with measurable imaging markers. Normal rats and rats that sustain a mild TBI will be imaged. Brain activation will be performed through tactile stimulation of the rat whiskers when their brain mitochondria function normally or impaired after mild TBI. The pharmacology-imaging model developed will be readily translatable to humans to better visualize therapy-induced brain reorganization during TBI rehabilitation.

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