NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

DIRECTORY OF GRANT AWARDS
2013 GRANT CYCLE

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

2013 GRANT CYCLE

DIRECTORY OF GRANT AWARDS FOR BRAIN INJURY RESEARCH

JUNE 2013

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 2013 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.

2013 MEMBERSHIP INFORMATION

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

Steven Levison, Ph.D. Grant Award: $537,500
UMDNJ – NJ Medical School

Project Title: *Improving Cell Replacement After Traumatic Brain Injury*

Pediatric TBI is a significant and under-appreciated problem. In the state of New Jersey the financial burden of pediatric TBI is approximately $20 million/year in hospital costs alone (NJCBIR Annual Report). Given the enormous financial burden, the emotional burden placed on caregivers and the fact that injury evolves differently in children than adults; there is strong rationale to study pediatric TBI.

Ideally, one would want to identify a therapeutic that would both preserve injured neurons and stimulate the replacement of those neurons and glia that had been irreversibly damaged. The goal of this project is to study the regeneration of new brain cells from the precursors that reside in the Subventricular Zone (also known as the "brain marrow") in a mouse model of pediatric TBI. Furthermore, we will test the effects of a therapeutic growth factor to determine whether the intranasal delivery of this growth factor will both reduce the extent of brain damage and also stimulate regeneration from the stem cells in the brain marrow. Analyses will be performed at the molecular, cellular, systems and behavioral levels to assess the ultimate success of our intervention.

Our ongoing studies indicate that the neural precursors of the Subventricular Zone are activated by traumatic brain injury and that their activation coincides with an increase in the growth factor, LIF, which is known to increase the production of new neural stem cells. But, the stem cell response is short lived (as is the increase in LIF); therefore, a primary goal of this research proposal is to more fully define which precursors are activated by traumatic brain injury, to establish the mechanisms that regulate their responses to injury and to test the therapeutic efficacy of intranasally administered LIF, that we predict will both preserve damaged neurons and enhance the regenerative capability of the cells of the brain marrow.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

Loren W. Runnels, Ph.D.
UMDNJ – Robert Wood Johnson Medical School
Department of Pharmacology

Grant Award: $533,240

Project Title: *Role of TRPM7 in Traumatic Brain Injury*

The overall goal of my research is to understand how misregulation of ion homeostasis contributes to the injury and ultimate death of neurons following traumatic brain injury (TBI).

TBI from falls, traffic accidents, assault, and sports affects an estimated 12,000 people in the state of New Jersey annually. However, as of now there are no specific drugs that work very effectively to limit neuronal damage in the hours and days following TBI.

Ion channels are macromolecular proteins that span the lipid bilayer of cell membranes. Long recognized for their crucial role in generating and orchestrating the signals that drive the firing of neurons, their misregulation can change the concentration of ions, such as Ca2+, Mg2+ and Zn2+ in cells, thereby increasing the stress on already injured neurons.

In a landmark 2003 publication in the journal *Cell*, the TRPM7 ion channel was revealed to be playing a critical role in neuronal cell death. Due to TRPM7's involvement in this process, the channel has been proposed as a possible drug target for the treatment of TBI. Using the well-established lateral fluid percussion (LFP) model, our aim is to evaluate whether TRPM7 may be a suitable drug target for TBI by investigating whether mice lacking TRPM7, or one of its two critical functional domains experience less injury following TBI.

We will also isolate neurons from mice lacking TRPM7, or its critical functional domains and use the isolated neurons to study how the channel is affecting the concentration of ions following injury, levels of reactive oxygen species, and cell survival. By using this genetic approach we will determine whether TRPM7 is a bona fide drug target for TBI with the goal of establishing a rationale for future drug development for TBI.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

William Craelius, Ph.D.
Rutgers, The State University of NJ
Department of Biomedical Engineering

Grant Award: $539,000

Project Title: *Continuous Monitoring of Hemodynamic Autoregulatory Factors after Traumatic Brain Injury*

Traumatic brain injury (TBI) is a devastating event which affects up to 15,000 of New Jersey children and adults, and their families each year. About 1,000 of these individuals die each year, and approximately 175,000 New Jersey individuals are currently TBI survivors with disability.

After severe TBI, the brain commonly swells uncontrollably, causing further damage to function. There are treatments to prevent swelling, but it is difficult to predict when these should be applied, since we do not fully understand what triggers the swelling. As a result, treatment often comes too late, and patients suffer further damage or death.

This project seeks to develop a method to predict the swelling event, up to an hour before it happens. The research teams, including Neurosurgeons and Biomedical Engineers, have devised a monitoring device that will use modern information technology and historical data from previous patients to predict the likelihood of swelling in the near future. This intelligent device will help Physicians make informed decisions, thereby improving patient outcomes.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

Frances Calderon, Ph.D.
UMDNJ – NJ Medical School
Department of Neurology & Neuroscience

Grant Award: $539,733

Project Title: *Enhancement of Neural Stem Cell Survival and Transplantation Efficacy by Docosahexaenoic Acid and its Derivative NPD1 in Traumatic Brain Injury*

Traumatic brain injury (TBI) is one of the most common causes of death and disability in the United States: 220,000 hospitalizations, 52,000 deaths from head trauma, and 80,000-90,000 patients suffering from permanent disability each year.

TBI results in long lasting consequences on the cognitive ability of patients due to neuronal loss. Neural stem cells have emerged as an attractive therapeutic solution to repair the damaged brain. Despite significant progress in stem cell transplantation after brain injury, success has been limited mainly due to the low efficiency of grafted cell survival.

Here, we propose to investigate whether docosahexaenoic acid (DHA) – a natural nutritional supplement, frequently found in fish, and its derivative NPD1, can serve as potential candidates for improving the efficacy of neural stem cells transplantation in the injured brain. We will evaluate the beneficial actions of DHA and NPD1 supplementation in stem cells transplantation after TBI using a rat model of focal contusion.

We also hope to gain a better understanding of the cellular mechanisms by which DHA/metabolites can facility engrafting of stem cell after brain injury. The expected results may support a therapeutic value for DHA/NPD1 for TBI treatment.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

Smita Thakker-Varia, Ph.D.
UMDNJ - Robert Wood Johnson Medical School
Department of Biomedical Sciences

Grant Award: $360,000

Project Title: *Eprhin Signaling in Axon Regeneration for the Treatment of TBI*

In the U.S.A. every year, about 1.7 million people suffer brain injuries from traumatic events. Approximately 12,000-15,000 of those people are from New Jersey. About one-third of the injuries result in lifelong disabilities incurring immeasurable costs to the families and society. According to recent reports from the CDC, traumatic brain injury (TBI) contributes to about 30% of all injury-related deaths. TBI leads to many neurological defects including impaired learning and memory and motor function. However, no treatments to reverse the damage exist.

As the cellular processes and molecular factors underlying the pathology of brain injury are still unclear, it is important to define these mechanisms before specific therapies can be developed. Following TBI there is neuronal loss and axonal damage resulting in disruption of neural circuits. These damaged connections can be situated by regenerating axons. Inhibitors of axon regeneration are found in the brain, and we are proposing to study the function of one such family of molecules, Ephrins and their receptor, Eph. Using genetically modified mice that have specific Ephrin/Eph ligands and receptors deleted, we will evaluate axon regeneration and behavioral effects of TBI. These mice will also be crossed to other mice such that their neurons in cortex are labeled with a fluorescent protein, to facilitate visualization. Understanding the inhibitory role of this molecule will direct us in designing therapeutic approaches. Candidate pharmacological agents will also be tested to see if the performance in mice is improved after TBI.

As the most densely populated state with a high rate of automobile accidents, New Jersey is particularly devastated by incidences of TBI. Furthermore, the general population suffers financial consequences in supporting the victims of TBI. The pharmaceutical companies located in NJ will serve as a resource in advancing our research on Eph receptors to the next level, impacting many spheres in New Jersey.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

Jean Lengenfelder, Ph.D. Grant Award: $397,941
Kessler Foundation

Project Title: *Neural Substrates of Facial Emotion Processing in Individuals with TBI*

A significant number of individuals with TBI report difficulty maintaining personal relationships and social support. Previous research has demonstrated these challenges to be the result of impaired emotional processing in persons with TBI. Specifically, individuals with TBI are not able to recognize facial affect in others as well as non-injured individuals can. This can lead to difficulty in social and emotional functioning. While we know these impairments exist, we do not know why these impairments occur in TBI or how they can be treated. This study set out to answer this question.

We hypothesize that diffuse axonal injury (DAI: the primary damage in TBI) is responsible for damaging connections between regions essential for emotional processing. We will examine the extent to which emotional processing deficits in TBI are due to abnormalities in structural and functional connectivity in TBI, using 3 different neuroimaging metrics (Diffusion Tensor Imaging, resting-state Functional Magnetic Resonance Imaging, and fMRI during task performance).

We will investigate the damage to brain structures critical to emotional processing, and how they relate to brain activity during a task requiring emotional processing. By examining these three-imaging techniques we believe we can begin to understand the neural network underlying emotional processing impairments in TBI. The identification of this neural network can then be used in future research to identify effective rehabilitation techniques to improve emotional processing in persons with TBI.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

Jennifer Buckman, Ph.D.
Rutgers, The State University of NJ
Center of Alcohol Studies

Grant Award: $534,755

Project Title: *Developing a Comprehensive Clinical Profile of TBI in Concussed Athletes Using Advanced Statistical Approaches*

The Center for Disease Control and Prevention estimates that 173,000 nonfatal sports and recreation related traumatic brain injuries (TBI) are treated annually in the United States. College athletes are at particularly high risk for sports-related TBI due to the competitive nature of sports at this level. Treatment providers currently cannot accurately predict TBI symptom severity or recovery, yet some individuals with TBI experience sustained and debilitating symptoms while others are virtually symptom free.

The proposed research program seeks to find the best existing clinical symptom predictors of TBI severity and recovery rate in NCAA Division I athletes by assessing pre- and post-injury clinical, mental, and physical health symptoms.

The overall project will examine pre-injury data from approximately 1,000 Rutgers student athletes across three years, and post-injury data from approximately 300 incidents of mild, moderate, or severe TBI that are treated in the Rutgers Department of Sports Medicine. The goal is to identify an easily administered yet highly predictive assessment protocol that streamlines clinical assessment and begins to build objective guidelines for return-to-play decisions, as well as other life decisions.

This project has high potential "translation" impact, meaning that its results can be immediately applied to real world clinical decisions that affect the lives of student athletes at Rutgers who suffer TBIs and be shared with other colleges and high schools in New Jersey. It may also help improve the lives of others who suffer a TBI unrelated to sports.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

FELLOWSHIP RESEARCH GRANT RECIPIENTS:

Myka Ababon
UMDNJ – Robert Wood Johnson Medical School
Department of Neuroscience & Cell Biology

Grant Award: $100,500

Project Title: *Retinoic Acid Signaling, the Orphan GPCR, Gpr161, and Adult Brain Stem Cells*

Traumatic brain injury (TBI) is caused by sudden trauma to the head. Symptoms resulting from TBI can range from mild concussions to permanent debilitating disability. Another type of brain injury is stroke, which occurs when blood flow to the brain is blocked, either due to a blood clot (ischemic stroke) or a ruptured blood vessel in the brain (hemorrhagic stroke). In both cases, brain damage is irreversible and no known treatment exists.

Neural stem cells provide a therapeutic route to replace damaged neurons after brain injury. A specialized region in the adult forebrain known as the subventricular zone (SVZ) contains a population of these stem cells. Understanding the molecular mechanisms regulating the proliferation of these stem cells will help develop therapeutics to aid neurogenesis after brain injury.

Retinoic acid (RA) has been shown to enhance proliferation of SVZ stem cells. Gpr161, an uncharacterized receptor, also regulates proliferation of adult stem cells in the SVZ and spinal cord. Preliminary findings reveal that RA is sufficient to activate Gpr161 expression in neuronal cells.

This study aims to investigate whether RA and Gpr161 act together to regulate proliferation of adult stem cells. The long term goal is to manipulate these signaling pathways to enhance neurogenesis and stem cell proliferation after brain injury.

Finally, Gpr161 belongs to a class of receptors that are the targets of more than 50% of currently available drugs in the market. This makes Gpr161 an extremely amenable potential pharmaceutical target to activate SVZ stem cell proliferation after brain injury.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

Kate Fitzgerald
Rutgers, The State University of NJ
Department of Cell Biology & Neuroscience

Grant Award: $100,500

Project Title: *The Neuroprotective Effects of BDNF after TBI*

Traumatic brain injury (TBI) affects millions of people in the United States per year, and can change a life forever by causing severe functional deficits in the brain. Deficits occur because neurons, the cells responsible for communication in the brain, become damaged and are unable to communicate properly with other neurons. To communicate, neurons send and receive signals; receiving signals relies on certain features known as dendrites. If dendrites are damaged by mechanical or chemical means, such as after TBI, the neuron cannot function as it had previously. Widespread damage to many neurons leads to diminished overall functioning in the brain, which is manifested in severe cases of TBI.

As TBI is characterized by an immediate mechanical injury followed by a delayed chemical injury, our laboratory has developed methods to mimic both of these injuries. Previously, we have shown the effects of the chemical injury on neuron functionality, and this project will build on those results by also studying the mechanical component of TBI. Additionally, as several drugs recently failed clinical trials for protecting against this chemical injury, we will investigate the protective potential of brain-derived neurotrophic factor (BDNF), a growth factor also present in neurons that survive injuries. Our laboratory has previously shown that BDNF increases dendrite number. Thus, we hypothesize that BDNF will also increase neuronal electrical activity, and as it promotes survival, will protect neurons from damage by TBI.

We will evaluate changes in functionality using two non-invasive techniques: microelectrode array (MEA) technology and calcium imaging. The techniques are complementary to one another because MEAs allow for the activity of many neurons to be observed at once while calcium imaging provides detailed activity profiles of single neurons. Neuron morphology will also be taken into account as an additional parameter for evaluating BDNF's protection of neurons. Examining the protective effects of BDNF with regard to both morphology and functionality will provide a new direction for TBI research and potentially a new therapeutic target.

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

PILOT RESEARCH GRANT RECIPIENT:

Victoria Leavitt, Ph.D. Grant Award: $170,296
Kessler Foundation

Project Title: *A Randomized Controlled Trial of Aerobic Exercise to Improve Memory in TBI*

Aerobic exercise holds a multitude of health benefits. Studies in mice have shown that aerobic exercise improves memory, and increases the volume of the hippocampus, the brain's primary memory center. Only two studies to examine this have been conducted in humans, healthy elders and schizophrenia patients. There has never been an aerobic exercise trial in traumatic brain injury (TBI) patients looking at hippocampal volume and memory.

This project is a randomized controlled trial of aerobic exercise in persons with TBI. We have collected strong pilot data showing the efficacy of a 12-week program of aerobic exercise (stationary cycling), versus a control condition of stretching in memory-impaired multiple sclerosis patients. Like TBI, multiple sclerosis generally affects people in early adulthood, and memory impairment is a cardinal symptom.

The primary goals of the proposed intervention are to: a) increase hippocampal volume, and b) improve memory. Importantly, our pilot data also show benefits of aerobic exercise on the level of brain function. Specifically, we looked at 'functional connectivity,' which refers to how efficiently remote regions of the brain 'talk' to each other. After taking part in the aerobic exercise program for 12 weeks, greater connectivity was observed across brain regions. TBI is an ideal population to benefit from aerobic exercise, given the early age of diagnosis, which allows for benefits of aerobic exercise to be maximally realized in a population with sufficient neurofunctional reserve. The expected benefits of aerobic exercise (increased hippocampal volume, improved memory) from this intervention stand to have a meaningful impact on people with TBI, including improved health, productivity, independence, and quality-of-life. And, unlike current treatments for memory impairment (e.g., pharmacological agents, cognitive rehabilitation), aerobic exercise is a cost-effective, all natural, readily-available treatment for memory problems.

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