DIRECTORY OF GRANT AWARDS
2008 GRANT CYCLE

NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

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JUNE 2008

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 2008 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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COMMISSION PERSONNEL

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

Smita Thakker-Varia, Ph.D. – Principal Investigator
University of Medicine & Dentistry of New Jersey - Robert Wood Johnson Medical School
Grant Award: $495,000

Proposal Title: *The Role of BDNF Signaling in Traumatic Brain Injury*

In the U.S.A. every year, about 1.4 million people suffer brain injuries from traumatic events out of which approximately 12,000 people are from New Jersey. About one third results in lifelong disabilities incurring immeasurable costs to the families and society.

Traumatic brain injury (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.

Immediately after TBI several growth factors are secreted. We are proposing to study one such growth and survival factor, brain-derived neuroptrophic factor (BDNF) and its receptors. This factor normally promotes neuronal and oligodendrocyte development and neuronal survival, as well as fosters learning and memory. In contrast, recent reports suggest that BDNF may have damaging effects depending on its structure or the receptor type to which it binds. BDNF levels are dramatically increased immediately after TBI, but which form of BDNF and which receptor types are induced, have not been studied. Furthermore, how these changes in the levels affect the progression of recovery from brain damage needs to be elucidated. By deciphering and manipulating the neurotrophin and its receptor signaling pathways, we hope to improve the deficits associated with TBI. In this project we are systematically studying the role of BDNF signaling using animals subjected to a model of TBI and examining changes in levels of different forms of BDNF and its receptors. In addition, using genetically modified mice that have specific receptors deleted, we will evaluate biochemical and behavioral effects of TBI in these mice. Understanding whether BDNF acts as a positive or a negative regulator of recovery will direct us in designing therapeutic approaches. As the most densely populated state with a high rate of automobile accidents, NJ 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 BDNF to the next level. The present project devoted to understanding the role of a promising molecule, BDNF, will therefore impact many spheres in New Jersey.

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John W Glod, M.D., Ph.D. – Principal Investigator
University of Medicine & Dentistry of New Jersey - Robert Wood Johnson Medical School
Grant Award: $330,000

Proposal Title: *The Role of the Bone Marrow Cells in Repair of the Blood Brain Barrier after Injury*

The repair of damaged blood vessels is an important component of the healing process after traumatic brain injury. Recent evidence suggests that cells from the bone marrow play an important role in the process. However, their precise function is not known.

This proposal will investigate how macrophages and mesenchymal stromal cells participate in blood vessel repair after brain injury and will begin to more specifically define their role in this process. A better understanding of the role of these cell types in this process will allow for the design of treatments to facilitate the repair of damaged vasculature that may improve the outcome of patients with traumatic brain injury.

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Peter Dowling, M.D. – Principal Investigator
Veterans Bio-Medical Research Institute, Inc.
Grant Award: $489,523

Proposal Title: *Novel Erythropoietin-derived Peptides for Treatment of Acute Brain Injury*

Twelve thousand new brain injuries occur each year in New Jersey and traumatic brain injury is often a devastating condition with long-term consequences. Effective treatment for patients with acute brain injury is a pressing need. We have developed a library of erythropoietin (EPO) derived small peptides and found that they have substantial neuroprotective effects in animal models of human multiple sclerosis. These novel small peptides can be administered for long periods of time compared to therapy with full length EPO because in contrast to full length EPO the small peptides exert their tissue protection without causing the side effects caused by an excessive increase in red cell mass, clots, stroke and possibly death. We plan to compare the effects of our small EPO peptides to full length erythropoietin therapy on modifying the clinical and histopathologic outcome in wild type C56 BU6 mice after traumatic brain injury. We will determine the therapeutic window for achieving a beneficial effect with our new peptides.

Our long-term objective is to determine if our small EPO peptides have a beneficial effect on acute traumatic brain injury and to define the mechanism(s) by which both small EPO-peptides and full length EPO modulate favorably effect acute brain injury. Since, in contrast to full length EPO, these small EPO-derived peptides can be administered for long periods of time without provoking any increase in red cell mass, they may hold immense potential for clinical application in both the early and late treatment of acute brain injury.

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Wilma J. Friedman, Ph.D. - Principal Investigator
Rutgers, The State University of New Jersey
Grant Award: $495,000

Proposal Title: *Brain Inflammation Leads to Neuronal Cell Death*

Brain injury represents a devastating change in the life of the patient, potentially resulting in loss of brain function and a continuing reliance on expensive, specialized health care.

In order to maximize the effectiveness of potential regenerative therapies, we need a thorough understanding of the mechanisms by which cells die after brain injury. If cell death following injury can be attenuated, there may be greater capacity for sparing of function and regeneration. Inflammation occurs in the brain as a consequence of many types of injury. Although the types of injury may differ, there are common features of the consequent inflammatory process, which is induced by traumatic brain injury as well as seizures. Seizures frequently occur as a consequence of traumatic brain injury, and neuronal loss in the hippocampus has specifically been associated with post-traumatic seizures. One of the most potent inflammatory cytokines is interleukin-1 (IL-1), which is induced by traumatic brain injury as well as seizures. Post traumatic brain injury can be attenuated by inhibition of IL-1 production.

One of the consequences of inflammation is the induction of receptors that mediate neuronal cell death, including the p75 neurotrophin receptor (NTR). The mechanisms that regulate expression of this death receptor on neurons after injury are unknown, however, since p75NTR is induced after many different types of injury, we suggest that there may a common mechanism due to the inflammatory process that occurs after all types of injury, such as the production of IL-1, that causes the induction of this receptor as well as increased production of the ligand, proNGF. Understanding the mechanisms of p75NTR regulation, and production of proNGF, after injury would provide critical information regarding an important mechanism of neuronal loss. Interference with the induction of p75NTR or with the p75-mediated cell death pathway may be a method of increasing neuronal survival after brain injury.

The goal of these studies is to define the mechanisms by which the p75NTR is upregulated in hippocampal neurons after injury, and to investigate the regulation of the ligand, proNGF, that elicits neuronal loss via p75NTR. These studies will provide insight into mechanisms causing progressive neuronal loss after brain injury.

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Martin Yarmush, Ph.D. - Principal Investigator
Rutgers, The State University of New Jersey
Grant Award: $327,275

Proposal Title: *A Novel Organotypic Model of Traumatic Brain Injury*

It has long been recognized that traumatically induced injury can result in wide-ranging damage to axons that form long-distance connections between different parts of the brain.

We propose to provide researchers working in the field of traumatic brain injury with an in vitro model that allows real-time and long-term evaluation of molecular and functional events in the axons following mechanical deformation. In order to follow the course of axonal response to injury over long-term (days or weeks), the model will incorporate the ability to monitor molecular, morphologic, and functional changes in axons of live brain tissue in a dish. We propose to accomplish this by employing a method that permits the maintenance of slices from the mouse brain ex vivo for prolonged periods of time. We will place these organotypic slices in conditions that induce axon sprouting outside the slice border. Axons are then easily visualized with microscopy for tracking morphological and molecular changes. Since these axons spontaneously form functional connections with another slice placed on the same culture substrate, these axons are an excellent model of the axons in the intact brain. By employing microfabrication and soft lithography techniques, we will develop a platform that can localize applied mechanical deformation to the axonal compartment of neurons only, or even to a pre-defined point along a particular axon bundle. A researcher using this platform will then be able to assess the axonal damage separately from the general tissue mechanical damage, and apply several deformation amplitudes to different axon bundles originating from the same tissue for high-throughput studies. Furthermore, we will develop the methodology to place organotypic tissue/microchannel network platform on a multiple electrode array (MEA) for experiments where assessment of the axonal function is required. By integrating the electrode array into the culture substrate, we will gain the ability to monitor the axons electrophysiologically, without disrupting the cultures, and ensure recordings from precisely defined locations over long time periods. The sophisticated in vitro model of TBI proposed in this application will enable novel and well-controlled experiments aimed at understanding and treating the axonal component of TBI, speeding up the rate of development of new treatments for TBI patients.

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MULTI-INVESTIGATOR PROJECT GRANT AWARDS:

Bonnie L. Firestein, Ph.D. – Program Director
Rutgers, The State University of New Jersey
Grant Award: $1,980,000

Proposal Title: *Treating TBI via Astrocyte-based Approaches*

During traumatic brain injury, cells in the brain are mechanically damaged due to the trauma of injury. A bit later, the cells are further damaged by a chemical called glutamate, which is released at high levels around the injury site. Our project tries to reduce the toxic effects of glutamate. Previous studies in our laboratories and other laboratories show that supporting cells, called astroglia, that are present in brain playa role in protecting neurons from glutamate-induced damage. In fact, the astroglial cells produce a protein called EAAT-1 that helps to remove glutamate from the area surrounding the neuron. Thus, production of EAAT-1 can block glutamate damage. Based on our preliminary data, we hypothesize that when astroglia produce extremely high levels of EAAT-1, neurons will be protected from glutamate released when the brain is injured. In addition, astrocytes release extra glutamate after injury, making the situation worse. As such, we will take a multi-technique approach to test if a natural compound found in the body called uric acid promotes a positive outcome after TBI since uric acid increases EAAT -1 on astroglia. We will also test to see if blocking glutamate release from astrocytes, using a drug, promotes positive outcome after TBI. We will use a cell culture model and mouse model of injury and bring together the expertise of researchers at four universities. Our results will have direct value for those people who have had TBI, especially in NJ, where the lead institution on this project is located. Our hope is that the compounds that we are testing will yield positive results for treatment of humans. In addition, our models will allow for future screening of new drugs for the treatment of TBI.

Subproject 1 - *Synaptic Architecture Preservation by Uric Acid and P2Y1 Antagonists after TBI*

Bonnie Firestein, Ph.D.

The Firestein laboratory will work with the Wagner and Morrison laboratories in using the flexible array technology for studying if either uric acid or P2Y1 antagonists are protective in dissociated cultures either exposed to glutamate or stretch-mediated injury, simulating TBI. Moreover, the Firestein laboratory will provide a resource for the other investigators to examine changes in synapse formation and spine morphology after injury in vitro and in vivo, both with and without treatment. Acting as the point project for developing and testing the uric acid and P2Y1 antagonists in dissociated hippocampal cultures, the Firestein laboratory will integrate activities with both Drs. Wagner and Morrison and Dr. Meaney to bring the necessary in vitro technology to their laboratories.

Subproject 2 – *Uric Acid Prevention of Post Traumatic Brain Cell Death on Stretchable Electrodes* - Sigurd Weaver, Ph.D., Barclay Morrison, Ph.D.

One critical gap in existing in vitro models of traumatic brain injury is the difficulty to record neuronal network function after injury. In this project, a team from Princeton and Columbia will combine their skills to advance a truly novel technology - embedding flexible electrodes onto an elastic, transparent membrane. This 'stretchable multielectrode array' will allow the team to explore the functional changes in organotypic slice cultures from the cortex and hippocampus after injury. Moreover, this group will test the efficacy of the uric acid and P2Y1 antagonists using this model. Results from organotypic hippocampal slices will be compared to data from dissociated culture experiments (Subproject 1), and will expand on in vivo studies from Subproject 3 to address one important question - what is the therapeutic window for either treating cultures with uric acid or P2Y1 antagonists? It is important to note that dissociated cultures allows for study of individual cell components (Subproject 1) while organotypic culture allows for study when circuitry is preserved (Subproject 2), making this a highly intergrative approach.

Subproject 3 - *Gliocentric Control of Glutamate to Improve Outcome after TBI* - David Meaney, Ph.D.

The in vitro studies from Subprojects 1 and 2 are complemented by in vivo studies in this project to study the mechanisms of glutamate elevation in the extracellular space and how controlling astrocyte characteristics can lead to a reduction in neuronal death after injury. This project uses in vivo imaging and single cell recording to demonstrate (a) onset of astrocytic calcium oscillations after injury, (b) the activation of extrasynaptic glutamate receptors on neurons after injury, and (c) the change in receptor activation with either uric acid or P2Y1 inhibitor treatment. Data from neuroprotection studies will be integrated with the expertise from Subproject 1 to determine if the treatments improve the changes in synaptic morphology and dendrite architecture that appear after TBI. Subproject 2 findings will be useful to determine the potential therapeutic window for these treatments. Overall, we feel this multi-investigator project is a timely integration of different expertise areas across several labs, and will allow us to more rapidly discover the most effective methods for using uric acid and P2Y1 antagonists as significant therapeutic approaches for treating TBI. Furthermore, all projects "feed forward" to each other as well as "feeding back" to one another.

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Steven W. Levison, Ph.D. – Program Director
University of Medicine & Dentistry of New Jersey - New Jersey Medical School
Grant Award: $1,533,130

Proposal Title: *Stimulating CNS Regeneration after Traumatic Brain Injury*

The overall goal of this multi-investigator proposal is to produce strategies to enhance regeneration of brain cells and to promote recovery of function after traumatic brain injuries (TBI). In response to the Commission's charge, we have planned state-of-the-art research with the goal of producing treatments for traumatic injuries of the brain. The proposed studies will use well-established rodent models of TBI. Because all age groups incur traumatic brain injuries, we plan to assess TBI in pediatric, juvenile and adult animals.

Moreover, because there are many people who are already living with the consequences of TBI, we focus on novel therapies to promote regeneration for those dealing with earlier injuries. Leveraging recent progress in stem cell research, we will assess the capacity for resident stem cells as well as for transplanted stem cells to heal the damaged brain. In addition, we will evaluate the roles of the support cells of the brain in promoting or inhibiting regeneration. Importantly, we will correlate the extent of neural regeneration with measures of cognitive and motor function.

Our laboratories have generated significant preliminary data to support the feasibility of the individual projects and through bi-weekly group meetings beginning in April 2006, numerous collaborations have emerged. Indeed, each individual project describes experiments that extend beyond the scientific expertise of the Principal Investigator and which rely upon the scientific expertise of other members of the group.

This multi-investigator proposal has developed from the recruitment of researchers with a diverse range of expertise related to TBI in response to the Commission's request for proposals. A major strength of this application is that it brings unprecedented expertise to TBI research in the fields of development, regeneration, stem cells, inflammation, gene expression, animal models, neurology, and neurosurgery. This application includes 4 scientific projects and one core facility that are highly interdisciplinary and inter-related. The goal of the research is to identify cells or molecules that can be targeted for treatment. Together, the work proposed in this multi-investigator application provides a new approach to the investigation of TBI towards moving stem cell therapies from the bench to the bedside.

Subproject 1 – *CNS Regeneration after TBI from Transplanted Primary Neural Precursors* - Allen Maniker, M.D.

The possibility of recovery from traumatic brain injury (TBI) has been greatly enhanced by research using transplanted cells from the central nervous system (CNS). Early work demonstrated that transplanting fetal CNS tissue into adult brain-injured rats attenuated hippocampal cell loss and neurobehavioral deficits, but the use of terminally-

differentiated human neurons from neuronal cell lines (hNT or NT2-N cells) was less encouraging since they survived and integrated into the injured adult rat brain, but did not improve functional recovery. Some promising preliminary studies with neural stem cell lines show that transplantation within 24 hrs of an injury improves cognitive outcome. However, acute transplantation is not always feasible. Therefore, to address this as well as the needs of patients living with chronic disabilities, the present application seeks to compare outcomes from acute vs. subacute vs. delayed transplantation. Moreover, since immortalized stem cell lines like the ones we have used may cause tumors, the likelihood that such cells would be used to treat patients is low. Therefore, in the studies described below we propose to graft primary neural stem cells generated from fetal and early postnatal rat brains into adult rats after controlled cortical impact (CCI) and evaluate their ability to migrate, differentiate, survive and reverse behavioral deficits. The rationale for using primary cells is that in the future we predict it will be possible to derive similar donor cells from human embryonic stem cells.

Subproject 2 – *CNS Regeneration after TBI from Endogenous Neural Stem/Progenitors* – Steven W. Levison, Ph.D.

Our published studies have demonstrated that there is an increase in the numbers of neural stem/progenitors (NPs) in response to hypoxic/ischemic (H/I) injury in rats and mice. Moreover, new neocortical neurons are produced during recovery from traumatic brain injuries. Therefore, we hypothesize that controlled cortical impact injuries in immature animals will produce increased numbers of neural progenitors in the subventricular zone (SVZ) and that the SVZ is the source of new neocortical neurons seen in these animals.

Moreover, we hypothesize that the immature brain has a greater capacity for repair than the more mature brain. Should this latter hypothesis prove to be true, a long-term goal would be to better define the properties of the immature brain that endow it with greater plasticity with an aim towards reestablishing this plasticity for adults. Completion of the experiments will provide key insights into the extent to which there is neuronal replacement after traumatic injuries.

Subproject 3 – *The Role of Microglia in Recovery from Injury* - G. Miller Jonakait, Ph.D.

Within hours following traumatic brain injury (TBI), immunoreactive brain microglia are activated with concomitant production of inflammatory cytokines, chemokines and reactive oxygen species. The pathological consequences of this inflammation are well known: adult neurons and glia are killed and production of new neurons is curtailed. However, the ability of microglia to elaborate nerve growth factor, brain-derived neurotrophic factor, glial cell line-derived growth factor, insulin-like growth factor, growth factors of the interleukin-6, heparin-binding, and transforming growth factorbeta (TGFP) families, and the neurite-promoting factor thrombospondin have led to the notion that microglia may, in fact, be neuroprotective. Moreover, as shown by Levison (Subproject #2) as well as others, brain injury promotes proliferation, migration and differentiation of both endogenous and exogenous neural stem/progenitor cell

populations, leading to functional recovery. Others have shown that these salutary actions on adult neural precursors may be directed in part by microglia. Moreover, we and others have shown that a factor or cocktail of factors from microglia is able to promote neural differentiation from undifferentiated embryonic neural precursors. Thus, while microglia are notable agents of neural damage, they may also be necessary agents of recovery. The goal of the current project is to examine the restorative role of microglia, hoping to maximize this aspect of the microglial response.

Subproject 4 – *Control of Axonal Sprouting from Adult Neurons by Reactive Glia and Neural Stem Cell* - Ellen Townes-Anderson, Ph.D.

Sprouting by directly injured and nearby neurons is a consistent response to injury in the central nervous system (CNS). This early sprouting response has been called "a window of opportunity" for repair of the CNS (1). In most cases, however, sprouting does not result in successful axonal regeneration. The cause in part is a nonsupportive environment. Glial cells are intimately involved in the life cycle of nerve cells. During development they guide axons to their correct targets, secrete trophic factors to promote cell survival, and enhance synaptogenesis. These developmental activities may be recapitulated during regeneration, but not much is known about how glial cells interact with adult neurons during CNS repair. In vivo, glial scars are the sites of inhibition of regeneration but in vitro systems invariably utilize young neurons to assess growth inhibition by molecular components of the scars. It is now well established that young and adult neurons contain different intrinsic responses to injury. Thus, assays utilizing mature neurons are crucial to understand the injury response in adults.

We have developed an in vitro culture system that supports the sprouting and regeneration of neuritic processes by adult, fully differentiated CNS neurons. The neurons come from amphibian retina and include sensory, secondary, and tertiary cells, the retinal ganglion cells. We propose to use this system to test soluble factors from reactive glial cell populations, neural stem cell transplants, and from brain injury resulting from controlled cortical impact (CCI), on the growth of adult neurons. Our questions are i) whether factors secreted by reactive glia inhibit axonal sprouting by neurons after a traumatic brain injury, and ii) whether controlling glial cell activation can prevent this inhibition.

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