DIRECTORY OF GRANT AWARDS
2008 A GRANT CYCLE

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

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DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

JUNE 2008

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

This data was compiled in compliance with the New Jersey Commission on Spinal Cord Research's statutory mandate, N.J.S.A. 52:9E-1, "…to compile a directory of spinal cord 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 A 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 Spinal Cord Research.

Please feel free to contact the New Jersey Commission on Spinal Cord Research at P.O. Box 360, 369 S. Warren Street, Trenton, New Jersey, 08625. The Commission's office can be reached by telephone at 609-292-4055, by fax at 609-943-4213, or by e-mail at NJCSCR@doh.state.nj.us.

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

2008 MEMBERSHIP INFORMATION

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NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

Principal Investigator – **Andrew Pachner, M.D.**

UMDNJ-New Jersey Medical School
Department of Neuroscience
Basic & Clinical Science Grant
$378,532

Project Title: ***Spinal Cord Injury in MS: Biomarkers and Therapy***

The most common cause of spinal cord injury, other than that caused by trauma, is injury mediated by the immune response, of which multiple sclerosis (MS) is the most prevalent. Recent studies have demonstrated that disability in MS is most highly correlated with injury to, and eventual loss of, the main signal conducting element of the spinal cord, called the axon. Despite this knowledge, we still have very little information as to how best to evaluate axonal damage in immune-mediated spinal cord injury (ISCI).

The hallmark of MS is the production within the spinal cord and brain of a protein called antibody, a component of the immune response. Whether or not this production, called intrathecal antibody production or ITAbP, contributes to spinal cord injury is unknown.

We will use two animal models of MS, called Theiler's murine encephalomyelitis virus-induced immune-mediated spinal cord injury (TMEV-ISCI), and experimental allergic encephalomyelitis (EAE), to find the answer to the two puzzles of axonal damage and role of ITAbP. An important advantage of this disease in mice is that it uniquely models the progressive disability in MS, which is due to spinal cord axonal injury. By focusing our attention on disability and axonal damage in the animals, we will demonstrate that axonal injury and loss can be readily measured and analyzed, and that the disability in the mice will be directly correlated to the degree of axonal involvement. We will also show that ITAbP is directly correlated to axonal involvement. Finally, we will pave the way for treatment of spinal cord injury in MS by showing that interference with ITAbP will result in lessened disability.

This work will have direct relevance to human spinal cord injury. Our ability to accurately measure disability in the mice will mean that our findings will have direct implications for human disability. Increasing our knowledge of axonal injury will affect how spinal cord injury in humans is assessed. Our ability to measure and inhibit the production of antibody in the spinal cord will provide the needed background for effective therapy for human immune-mediated spinal cord injury.

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Principal Investigator – **Nosir Langrana, Ph.D.**

Rutgers, The State University of New Jersey
Department of Biomedical Engineering
Basic Science Grant
$393,158

Project Title: ***Neural Precursor Control by ECM for Spinal Cord Regeneration***

The emotional, physical and financial toll conveyed by traumatic injuries or diseases that damage the spinal cord is devastating to residents of New Jersey and the world. It is our hope that, through multidisciplinary efforts such as those described herein, we at Rutgers, and specifically the Department of Biomedical Engineering, can contribute to the quest for a cure for the effects of spinal cord injury. Biomedical Engineering represents the interface between engineering and medicine. The biomedical industry thrives in New Jersey, and we believe it is crucial that the BME department at Rutgers thrive as well, to infuse the industry with a topnotch, educated, homegrown workforce. The success of the program is linked to the success of its faculty.

Based on basic biomedical engineering research using hydrogels as scaffolds to bridge axon growth across a severed spinal cord and the potential to not only guide neuronal growth, but to control differentiation of stem cells and neural precursors that lie dormant in the adult central nervous system we are proposing further investigation that will ultimately enable us to implement strategies of ENGINEERING new tissue for spinal cord regeneration in vivo. The goal of this proposal is to optimize the characteristics of the biomaterial in vitro to induce axon regeneration through a hydrogel scaffold and physically grow axons by differentiating cells into neurons and supportive cells. An additional goal is to identify pitfalls and investigate alternatives for innovative tissue engineering strategies.

The goal of this proposal is to optimize mechanical characteristics of scaffold hydrogels in vitro to induce first expansion of NPC and then differentiation. It is probable that the mechanical stiffness necessary for each phase of growth is unique. The Specific Aims of this proposal are to control neural precursor proliferation and differentiation by extracellular matrix stiffness in two and three-dimensions.

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Principal Investigator – **Martin Grumet, Ph.D.**

Rutgers, The State University of New Jersey
W.M. Keck Center for Collaborative Neuroscience
Basic Science Grant
$342,064

Project Title: ***Acute Treatment of siRNA for RhoA in Spinal Cord Injury***

The enzyme Rho kinase, or simply Rho controls cellular functions including motility, growth, differentiation, apoptosis as well as modulation of blood brain barrier. The Rho pathway is activated and prevents axons from regrowing in the spinal cord following injury. Cethrin, a recombinant fusion protein reverses the activation of Rho and is currently in Phase IIa clinical trials, indicating the importance of Rho as a clinically relevant target for treatment of SCI. Another approach to inhibit the induction of Rho is to interfere or knockdown the cellular mechanism involved in its production by using short chains of genetic material termed as small interfering RNAs, or siRNA. The genetic material contained in these siRNAs can be made to match specifically a portion of the genetic material on the messenger RNA that is involved in the synthesis of the unwanted protein, resulting in less of the specific protein by deactivation of the mRNA that encodes it. We have recently found that validated siRNAs against RhoA improved functional recovery following spinal cord contusion in the rat using the 12.5 mm weight drop model of moderate injury. We propose to test the hypothesis that acute knockdown of RhoA improves recovery in rats following moderate/severe spinal cord contusion and determine mechanistic changes associated with locomotor improvements. We will analyze the effects of siRNAs against RhoA (siRhoA) in a mild (12.5 mm) spinal cord contusion. The results will reveal the timing of injury-induced activation of RhoA and the ability of siRhoA to inhibit induction of RhoA protein. Additionally, we will perform dose escalation studies to determine whether higher doses of siRhoA are more effective in the more severe (25 mm) spinal cord contusion. We will test effects of different doses of siRhoA on both acute blood-spinal cord barrier (BscB) dysfunction and locomotor changes. The combined results of the short- and longer-term effects of siRhoA on expression of the RhoA protein in different types of cells together with the effects on spinal cord histology and locomotor behavior will provide a cellular basis for interpreting the therapeutic actions of suppressing RhoA expression.

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Principal Investigator – **Melitta Schachner, Ph.D.**

Rutgers, The State University of New Jersey
W.M. Keck Center for Collaborative Neuroscience
Basic Science Grant
$395,870

Project Title: ***Spinal Cord Intrinsic Regulation of Regeneration-Proactive g***

Regeneration of neurons following spinal cord injury is generally believed to be inhibited by the glial scar at the site of injury, the generally inhibitory tissue environment of the adult central nervous system, and the intrinsic inability of some neuronal cell types to regrow their processes (axons and/or dentrites) after injury. In mammals and, in particular, humans, the glial scar and the inhibitory tissue environment are major impediments to neuronal regrowth and motor and sensory recovery after trauma. However, in zebrafish, a recognized biological model system benefiting from detailed genetic studies, neurons are able to regenerate and recover function after spinal cord injury, suggesting that the inhibitory elements characteristic of the adult mammalian central nervous system do not predominate. Our research has demonstrated that spinal cord injured zebrafish indeed regenerate specific neuronal tracts, and that this regeneration requires the neuronal expression of the adhesion molecular L1.1 and the extracellular matrix glycoprotein tenascin-C that make cells interact in a beneficial manner to foster regeneration. We believe that other genes are required for regeneration of neurons not only with regard to the "upstream" neurons the axons of which have been severed, but also in the environment that axons regrow into distal to the lesion site and at the lesion site. We can thus dissociate the intrinsic neuronal growth from surrounding spinal cord tissue in adult zebrafish. We will use DNA microarrays to identify specific genes expressed in the distal part of the lesioned spinal cord and at the lesion site. Our past studies with L1.1 and tenascin-C also demonstrate that we can block putative regenerative genes by adding morpholino antisense DNA molecules to injured spinal cords. These methods will allow us to demonstrate that a gene selected for its presence in the regenerating tissue participates in the regeneration process. These studies will identify new cellular processes that are necessary for regeneration. In complement with newly developed therapies to reverse inhibition in the central nervous system of mammals, the newly identified regeneration-associated genes represent attractive new targets for drug development or gene therapy in humans.

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FELLOWSHIP GRANT RECIPIENTS:

Principal Investigator – **Kedar Mahajan**

UMDNJ-New Jersey Medical School
Department of Neurology & Neuroscience
Basic Science Grant
$60,000

Project Title: ***IGF-1 Mediated Oligodendrocyte Progenitor Survival in SCI***

The goal of all spinal cord injury (SCI) research is to strive towards providing an individual with functional recovery and to help them achieve their maximum independence. Treatment needs to be tailored to how the spinal cord is injured since the type of damage varies. We will focus on the most common type of injury affecting NJ residents involving compression or bruising of the spinal cord seen in blunt trauma including motor vehicle collisions, falls, and assaults. In the United States, approximately 253,000 people were alive with SCI in June 2006 and since 2000, motor vehicle collisions account for 46.9% of reported SCI cases. In New Jersey, 80% of the new 257 cases of spinal cord injury in 2000 were attributable to transportation injuries, falls, and assaults.

In this type of injury, paralysis is mainly caused by indirect damage to nerves and not from the original mechanical force. Although some functional loss can occur from nerves that are cut, paralysis largely stems from a cascade of events (secondary injury) by decreased blood and oxygen to the tissue. Damaged cells and first responders to the site of injury release chemicals, like glutamate, that can be toxic in excess to healthy nerves and supporting cells. Even if a nerve is not cut, loss of its sheath during secondary injury will render it useless. Making the situation more problematic is the loss of "oligodendrocytes", which are cells that can repair the damaged nerve's sheath and restore function.

Oligodendrocyte progenitors (OPCs) are the precursors and source of all mature oligodendrocytes. Our previous data demonstrate that insulin-like growth factor I (IGF-I) is the only studied growth factor able to sustain long-term survival in OPCs from toxic levels of glutamate. The crux of our research is to understand how the IGF-I survival pathway we have previously characterized works at the cell surface of the OPC. The survival signaling necessary to protect OPCs would need to be robust, based on studies by others, and thought to occur in complexes at the cell surface called "lipid rafts". Based on our preliminary data, we first hypothesize that the IGF-I survival signaling molecules come together in rafts. Because increased vulnerability to glutamate occurs at different stages in oligodendroglial development, we also hypothesize that the survival complexes differ throughout the lineage and contribute to this vulnerability. To test our first hypothesis, we will investigate components of the IGF-I survival signaling in the cell membrane at distinct stages in oligodendroglial development. We will then study how disruption of lipid rafts affects the ability of IGF-I to promote OPC survival in the presence of glutamate. The proposed studies characterizing the IGF-I survival signaling pathway in the context of secondary damage may ultimately provide translational applicability in the design of therapeutics to promote remyelination and functional recovery.

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Principal Investigator – **Christopher Langhammer**

Rutgers, The State University of New Jersey
Department of Cell Biology & Neuroscience
Department of Biomedical Engineering
Basic Science Grant
$60,000

Project Title: ***Spinal Cord Motor Neuron-Based Neural Interface Design***

The ideal neural interface establishes two way contact between a technical device and neural structures within the body. The objective of such devices is to record bioelectrical signals originating in the nervous system, or to implant such signals, in order to restore motor and sensory function in disabled patients. Neural prostheses based on such neural interfaces are a largely unrealized opportunity to improve the quality of life for spinal cord injury patients. One subtype of device, named a neuromuscular prosthesis, captures neural signals controlling motor function and transmits them externally where they will be used to control an external device. Most efforts to design neural interfaces target cortical neurons in the primary motor cortex using penetrating multielectrode arrays (MEAs) meant to record depolarization of cell bodies. These devices have yet to perform at a level necessary to justify their use in large-scale clinical trials. Complicating issues for these electrodes include poor long-term recording due to fibrous encapsulation, inflammation, death of surrounding neurons, and insufficient understanding of neural information processing and control to correctly interpret signals recorded at their implantation site.

A modification of the known "cultured probe" design, a neural interface in which neurons cultured directly onto an electrode surface prior to implantation facilitate incorporation into the host nervous system, may significantly improve the recording capabilities of current neural interfaces. By using muscle cells (myotubes) rather than neurons as the electrogenic cell type cultured onto the electrode surface and by targeting the peripheral nervous system (PNS) as the implantation site, many of the roadblocks to progress in this field can be overcome. This project combines single celled electromyography which takes advantage of myotubes' large depolarization relative to neurons, with a cultured probe technique which takes advantage of the high degree of specificity available to dissociated cultures grown on MEAs. The myotubes have the added benefit of naturally encouraging the ingrowth of damaged motor axons using naturally secreted cell signaling molecules. Our hope is that this regenerative capacity can be used to target the growth of damaged spinal neurons into an electrode, which captures and redirects the motor signal contained therein.

We are using cultured myotubes as a biological signal amplifier, enabling us to tap the neural signals encoding motor intention in PNS axons. Using the myotube cultured probe technique; we hope to design an electrode that improves the robustness of neural interface recording without sacrificing the resolution associated with implanted electrodes.

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Principal Investigator – **Marton Toth, Ph.D.**

Rutgers, The State University of New Jersey
Department of Molecular Biology & Biochemistry
Basic Science Grant
$100,000

Project Title: ***Molecular Mechanisms of Neuroprotection and Regeneration***

In the complex scenario of spinal cord injury, there are two major problems that need to be addressed in order to limit long-term debilitation. First, although some neurons may be physically damaged by initial impact, many other die during secondary necrosis induced by exacerbated ion channel activity. Blocking or delaying secondary neuronal necrosis would significantly limit consequences of injury. The second problem is that CNS neurons do not regenerate. Regeneration is complex, and a clear understanding of factors that impact regeneration proficiency are essential as we move toward effective strategies that encourage regeneration. My work constitutes very basic research on the biology of these two problems.

The Driscoll lab uses uniquely applied experimental approaches in the C. elegans model system to identify genes that impact neuronal necrosis and genes that regulate regeneration. In this model we have the ability to easily manipulate genes, to observe labeled neurons directly and to perform axotomies on single neuronal fibers in vivo. Since most basic biological processes, including cell death and neuronal regeneration, are conserved from nematodes to humans, we can decipher the basic molecular rules of a given process in C. elegans and then use this information to address the function of related molecules (homologs) in humans.

My first goal is to characterize and identify genes that are protective against ion channel hyperactivation-induced necrosis. Necrotic cell death initiated by ion channel hyper-activation plays a major role in the initial and prolonged death of neurons consequent to injury. Previously, our lab collected mutants that enhance necrosis that is induced by channel hyperactivation. Since the loss-of-activity enhances, we infer that the normal activity of the impacted genes must be neuroprotective. I will identify 1-2 of these genes and conduct experiments that begin to reveal how they confer neuroprotection. My findings could be extrapolated to suggest working hypotheses for limiting human neuron loss in traumatic injury.

My second goal is to test the impact of modulating glutamate signaling on the capacity for neuronal regeneration after laser-directed axotomy of single glutamatergic neurons in vivo. Excitatory glutamate (Glu) signaling is dramatically dysregulated consequent to SCI, but little attention has been given to the impact of (Glu) on proficiency for neuronal regeneration. Based on observations in the mammalian literature, I propose that high (Glu) may be a significant factor in the impediment to early neuronal regrowth in SCI. I will elaborate mechanisms of Glu impact on regeneration in vivo by modulating glutamatergic signaling molecules in a C. elegans model and performing laser axotomies. The anticipated outcome of this line of study is the provision of the first detailed evaluation of how the molecules of glutamatergic signaling can contribute to neuronal regeneration proficiency of glutamatergic neurons.

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