DIRECTORY OF GRANT AWARDS
2010 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 2010

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 2010 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.

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Peter W. Carmel, M.D.
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NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

James Millonig, Ph.D. – Principal Investigator
University of Medicine & Dentistry New Jersey-Robert Wood Johnson Medical School
Grant Award: $600,000

Proposal Title: *Orphan GPCR, Gpr161, A Regulator of Spinal Cord Development*

Spinal cord injury afflicts ~250,000 individuals in the US. The resulting damage often leads to quadriplegia or paraplegia, and loss of neural function posterior to site of damage. A developmental disorder of the spinal cord is spina bifida, where the neural plate does not fold properly into the neural tube. Spina bifida affects approximately 1 in every 1000 live births. Affected individuals have numerous neurological deficiencies including paralysis.

Stem cell therapy provides a potential therapeutic route to replace lost or damaged neurons for both spinal cord injury and disease. Recently, an endogenous spinal cord stem cell population has been characterized. These stem cells are situated around the central canal and require a cell biological process call epithelial-mesenchymal transition (EMT) for their survival. Interestingly, EMT also regulates neural tube closure.

Our previous research has identified an uncharacterized receptor called Gpr161 that is expressed in the neural folds and adult spinal cord stem cell population. Preliminary data indicate the receptor regulates EMT. The goal of this proposal is to investigate whether Gpr161 regulates EMT during neural tube closure and in the adult spinal cord stem cells by examining two mouse Gpr161 mouse mutants.

These studies will provide insight into molecular mechanisms responsible for spina bifida and will further characterize the pathways needed for adult stem cell survival. Our long-term goal is to manipulate these molecular and cellular pathways so spina bifida can be prevented and the spinal cord stem cell population can be developed as a cell based therapy to treat spinal cord injury.

Contact Information:
James Millonig, Ph.D.
UMDNJ-RWJMS
Neuroscience Department
679 Hoes Lane
Piscataway, NJ 08854
millonig@cabm.rutgers.edu
732-235-3391

Li Cai, Ph.D. – Principal Investigator
Rutgers, The State University of New Jersey - Biomedical Engineering
Grant Award: $600,000

Proposal Title: *Non-Coding DNA Sequence in Oligodendrocyte Development*

Preceding the development of therapeutic strategies for spinal cord injury is an identification of those pathological processes that might serve as therapeutic targets. Oligodendrocytes are the myelin-forming cells in the brain and spinal cord; they are essential for axonal conductance and crucial for proper neuronal function; and thus, they are important clinical targets for restoring function after central nervous system (CNS) injury, particularly spinal cord injury.

Demyelination has been documented as a component of spinal cord injury in several species including humans. Remyelination appears to be one of the most feasible restoration strategies. The goal of this project is to determine the role of regulatory DNA sequences and their interacting protein factors during oligodendrocyte-lineage development as future potential therapeutic targets. Olig2 gene, a basic helix-loop-helix transcription factor, has been demonstrated to be essential for the differentiation of neural stem cells into mature myelinating oligodendrocytes as well as motoneurons. Lack of Olig2 expression in mutant mice leads to the complete loss of oligodendrocytes and motoneurons, while exogenous Olig2 expression in neural stem cells leads to the generation of oligodendrocytes. Although the functional roles of Olig2 during neural development have been revealed, the transcriptional regulatory mechanism that controls Olig2 expression is largely unknown. A key component in transcription regulation of gene expression is cis-regulatory elements, e.g., enhancers, non-coding DNA sequences that are often evolutionarily conserved. Upon binding of trans-acting factors, enhancers determine tissue or cell type-specific expression of particular genes. The requirement of Olig2 in both oligodendrocyte and motoneuron lineage development indicates that different types of enhancers may exist to regulate motoneuron- versus oligodendrocyte-specific Olig2 expression. Recently, an enhancer that regulates the motoneuron lineage-specific Olig2 expression (motoneuron-enhancer) has been identified; however, enhancers that regulate oligodendrocyte lineage-specific Olig2 expression (oligodendrocyte-enhancers) have yet to be identified.

We, therefore, hypothesize that evolutionarily conserved non-coding genomic DNA sequences are essential in oligodendrocyte cell fate specification by regulating Olig2 expression. The current proposal is aimed at testing this hypothesis by identifying novel oligodendrocyte-enhancers and determining their specific regulatory functions to elucidate the molecular mechanism of oligodendrocyte cell fate development. Successful completion of the proposed project is expected to provide novel understanding of the contribution of non-coding DNA elements (enhancers) to oligodendrocyte-lineage development. Novel enhancers and trans-acting protein factors identified in this project should provide potential targets and help the development of therapeutic strategies for patients with demyelinating diseases such as spinal cord injury.

Contact Information:

Li Cai, Ph.D.
Rutgers - Biomedical Engineering
599 Taylor Road
Piscataway, NJ 08854
lcai@rutgers.edu
732-932-0165

EXPLORATORY RESEARCH GRANT RECIPIENTS:

Bharat Biswal, Ph.D. – Principal Investigator
University of Medicine & Dentistry New Jersey-New Jersey Medical School - Radiology
Grant Award: $198,120

Project Title: *Altered Brain Connectivity in SCI Patients Using fMRI*

Spinal cord injury remains a major source of disability with enormous economic consequences and health related issues. Spinal cord injury (SCI) is an insult to the spinal cord resulting in a change, either temporary or permanent, in its normal motor, sensory, or autonomic function. The most common causes of SCI in USA are motor vehicle accidents (44.5%), falls (18.1%), violence (16.6%) and sports injuries (12.7%). The incidence of traumatic SCI in the United States is 10,000 cases per year in the United States with a total of 400,000 to 450,000 individuals living with this type of injury. SCI has major functional, medical and financial effects on the injured person, as well as an important effect on the individual's psychosocial well-being. As per a study (Berkowitz M et al, 1998) SCI-related cost in the USA was estimated $9.7 million per year.
In New Jersey alone, approximately 300 new injuries occur each year. Each patient with spinal cord injury is given a number of behavioral and physiological tests to asses the severity of the injury, and the chance that rehabilitation will improve the outcome for each case. While most of the therapies are aimed at improving the motor function, it is assumed that the brain motor function remains intact. This assumption has recently been challenged showing that patients with spinal cord injury have different brain function than that of matched controls. This project is aimed at extending these results using a number of different tasks, and by using a greater patient population that would lead to greater certainty of the results. Further, other regions that may be affected will be also determined.

fMRI because of its high spatial and temporal resolution in addition to its non-invasiveness has fast become the method of choice for studying human brain function. fMRI is thus currently being used in a number of clinical populations to quantify how brain networks are different between patient populations and healthy controls.
The New Jersey Medical School is one of only handful of research institutions with a research dedicated high-filed 3T MRI human scanner. In this exploratory project, innovative experimental tasks and data analysis methods have been proposed which in addition to providing new result; will also provide data to conduct a larger sample fMRI study on SCI patients. The PI (Biswal) is trained in Biophysics, and is currently funded by the NIH to study TBI subjects using fMRI. Dr. Lee is a neuroradiologist with expertise in clinical fMRI. Dr. Foulds is an expert on rehabilitation and biomedical instrumentation. Dr. Khubchandani has several years of experience in MRI. In this project we anticipate to reliably determine the resting cerebral blood flow and metabolic changes both during rest and during a number of different stimulus conditions. Comparisons will be made between patients with SCI and matched controls to determine significant difference in brain function.

Contact Information:
Bharat Biswal, Ph.D.
UMDNJ-NJMS - Radiology Department
ADMC Bldg. 5, Room 575
30 Bergen Street
Newark, NJ 07103
bbiswal@yahoo.com
973-972-7498

Patricia Buckendahl, Ph.D. – Principal Investigator
Rutgers, The State University of New Jersey - Center of Alcohol Studies
Grant Award: $200,000

Project Title: *Role of Osteocalcin in Spinal Cord Injury*

Spinal cord injury (SCI) is very costly. The average age for SCI is 21.6 years. Some are injured in military service, others in traffic accidents, sports activities, construction accidents, etc. The current lifetime medical care is nearly $1 million dollars for each patient. The average new patient can expect to live for about 60 years after the injury, making health following injury particularly important for a productive life.

Acute, severe bone loss occurs in paraplegic SCI patients, accompanied by decreased bone formation rate and an even greater increase in bone degradation. The resulting weakened bone has a high fracture rate that increases yearly. The extra medical care associated with bone fractures and their complications uses significant financial resources. Treatments to increase bone mass in the SCI patient would reduce the fracture rate, associated pain, and the damage to the health of the patients.

Osteocalcin (OC) may be involved in bone preservation following SCI, and play a role in recovery. This bone-related calcium binding protein is deposited in mineralizing bone matrix. It is synthesized in proportion to bone formation, with about 10% being released directly to plasma in a reflection of bone formation. In addition to its probable function in mediating bone formation rate, OC has been implicated in glucose regulation, stimulating insulin secretion and reducing insulin resistance. The current proposal tests hypotheses regarding the role of OC in bone integrity following SCI and its potential role as a neuroactive protein in the functional recovery from SCI.

Our overall aim is to demonstrate that the OC null mutant mouse (knockout, KO), which has no osteocalcin in bone or circulation, has greater bone loss than its normal, wild-type counterparts (WT). We will compare KO and WT mice subjected to either SCI or sham surgery (all procedures except cord injury), evaluating the effects of SCI on recovery of movement, pain sensation, and commonly used plasma indicators of bone formation and degradation. We will also evaluate expression of genes related to pain sensation and bone metabolism. The amount of bone present in limbs and spine will be quantified post-mortem by microCT (a small version of the clinical “CAT-scan”), and by histomorphometry similar to methods used in bone biopsies. We will quantify these parameters in KO and WT mice, first following standard SCI, and second in mice supplemented with native OC to determine if OC counters the effects of SCI.

The proposed studies will establish the importance of OC in the loss of bone density in the affected bones following SCI and in the functional recovery from SCI. Insight gained into possible functions of OC in these processes will advance the understanding of bone loss following SCI, will lead to improvements in the post-injury treatment of SCI and in the lives of the patients, and will have a significant economic impact.

Contact Information:

Patricia Buckendahl, Ph.D.
Rutgers - Center of Alcohol Studies
607 Allison Road
Piscataway, NJ 08854
buckendp@rci.rutgers.edu
732-445-3590

Lei Yu, Ph.D. – Principal Investigator
Rutgers, The State University of New Jersey - Genetics & Center of Alcohol Studies
Grant Award: $200,000

Project Title: *Spinal Cord SIP30 Mediates Injury-Induce Neuropathic Pain*

Chronic pain from nerve injury can be life-long, is rather common, and represents a major public health problem as well as an unmet medical need. We used a rodent model of neuropathic pain and identified a molecule called SIP30 that plays a role in mediating injury-induced neuropathic pain.

In this project, we would like to study whether sustained pain relief can be achieved by inhibiting SIP30 activity in the spinal cord. This project is relevant to spinal cord research, because spinal cord is the primary site for sensing pain, thus a potential site for therapeutic intervention in pain relief, especially for neuropathic pain.

Contact Information:

Lei Yu, Ph.D.
Rutgers - Genetics &
Center of Alcohol Studies
607 Allison Road, Room 215
CAS-215, Smithers Hall
Piscataway, NJ 08854
lei.yu@rutgers.edu
732-445-0794

FELLOWSHIP GRANT RECIPIENTS:

Robert O'Hagan, Ph.D. – Principal Investigator
Rutgers, The State University of New Jersey - Human Genetics Institute
Grant Award: $150,000

Project Title: *The NNA-1 Carboxypeptides and C. Elegans Neuroregeneration*

Although neurons in the mammalian central nervous system (CNS) possess an innate ability to regenerate, this ability is often insufficient to regain function after spinal cord injury. Neurons have molecular motors that travel along cellular tracks called microtubules (MTs); these motor and tracks are clearly important for outgrowth and regeneration of neurons. A clear understanding of how these molecular motors and MT-based transport are regulated during regeneration is important for development of improved therapies to encourage regrowth of spinal cord neurons that have been injured. One mechanism—post-translational modification of MTs—is coming into view as a means of regulating the activity of motor molecules in neurons. Detyrosination--removal of a tyrosine amino acid--is a post-translational modification that labels stable MTs. Molecular motors have preferences for specific modifications of MTs, suggesting that there is a "tubulin code" that guides various kinesin and dynein motors to transport their cargoes to specific subcellular locations. For example, kinesin-1 motors are excluded from dendrites in mammalian neurons because of a preference for detyrosinated MTs, which are more prevalent in axons. However, the identity of the enzymes that detyrosinate MTs have remained unknown. Furthermore, a role for this mechanism in neuronal regeneration after spinal cord injury has not yet been explored.

Nna1 (nervous system nuclear protein induced by axotomy), a cytosolic enzyme, is predicted to detyrosinate MTs. Nna1 gene expression is activated by spinal cord injury, with expression continuing during regeneration and outgrowth of axons until target reinnervation. A mutation in the gene that encodes Nna1 causes neurons to degenerate and die in pcd (Purkinje cell degeneration) mutant mice, highlighting the importance of this gene in the CNS. However, evidence that Nna1 detyrosinates MT is lacking.
The microscopic worm Caenorhabditis elegans has a homologous gene called nna-1. Mutations in this gene cause defective neuronal transport of the receptor ion channel protein PKD-2 and the motor protein KLP-6, but not another motor protein called OSM-3. A change in the tubulin code in C. elegans neurons might explain the defects in nna-1 mutants.

I propose to investigate the function of NNA-1 in C. elegans. I will determine the expression pattern of NNA-1 and find out if NNA-1 colocalizes in vivo with MTs or various motor proteins in C. elegans neurons. I will determine if C. elegans NNA-1 expression is activated by lesioning neurons and if NNA-1 plays a role in neuronal regeneration. I will also test biochemically if NNA-1 detyrosinates MTs in vitro. I will also determine if loss of NNA-1 function alters localization or motility of a panel of fluorescently-tagged motor proteins in vivo. The overall goal of this project is to determine if NNA-1 produces a tubulin code and the role it plays in regeneration after neuronal injury.

Contact Information:
Robert O' Hagan, Ph.D.
Rutgers - Human Genetics Institute
145 Bevier Road
Piscataway, NJ 08854
ohagan@biology.rutgers.edu
732-445-1027 X40069

Jeffrey Fox – Principal Investigator
Rutgers, The State University of New Jersey - Chemical & Biochemical Engineering
Grant Award: $60,000

Project Title: *Optimized Synergistic Cues to Facilitate Spinal Cord Repair*

Thousands of people are affected by spinal cord injuries every year, and there are currently no clinical methods to overcome the potentially devastating effects. Though much research has been directed toward promoting nerve cell regeneration and direction, little research has focused on guiding other cells which may inhibit or support this process. In attempting to repair nerve damage, it is important to consider all cell types at the injury site, not just nerve cells. For example, at the injury site cells known as astrocytes are a primary contributor to the formation of scar tissue, which is one of the greatest barriers to neuronal reconnection. Most research has focused on inhibiting astrocyte function; however, this project focuses on directing astrocytes away from the immediate injury site in an attempt to prevent scar tissue from forming and inhibiting the healing process.

The long-term goal of this research is to develop an implantable device with properties optimized to promote and direct nerve cell regeneration such that spinal cord injuries may potentially be repaired. This project will support the overall goal by evaluating three specific facets which may be incorporated in an implantable device. The first and second are to direct astrocyte migration in a gelatin network by varying the degree of network stiffness and the concentration of molecules that support astrocyte adhesion. Previous research has shown that astrocyte migration and nerve cell growth are affected differently by these two facets. For example, astrocyte movement is better in the presence of higher stiffness, while nerve growth is greater when stiffness is lower. Once optimum conditions to direct astrocyte movement have been determined, they will be established with nerve cells present to assess and further modify the system as required. We will attempt to align the astrocytes in parallel with nerve cells instead of in front of them with the hope that astrocytes may be induced to provide beneficial effects instead of detrimental ones. New Jersey citizens can only benefit from this type of research since the state's biotechnology and pharmaceutical industries are uniquely positioned to transform the results into a functional device. This translates into more jobs in the state, increased business revenue, and higher tax revenue.

Contact Information:
Jeffrey Fox
Rutgers - Chemical & Biochemical Engineering
599 Taylor Road, Bldg. #3893
Piscataway, NJ 08854
jefffox@rci.rutgers.edu
732-445-4500 X6359

Eunchan Park, Ph.D. – Principal Investigator
Rutgers, The State University of New Jersey - Waksman Institute
Grant Award: $150,000

Project Title: *Neuronal Signaling in Response to Hypoxia*

Spinal cord injury (SCI) is a distressing illness that results in the loss of sensory and motor function. Affected individuals often experience chronic neuropathic pain and the loss of mobility, sensation, and autonomic function. During SCI, neurons are damaged both mechanically and by hypoxia (O2 deprivation caused by the traumatic breakdown or obstruction in the blood vessels that supply the spinal cord neurons). The initial events are often restricted to a small region of the spinal cord; however, hypoxic neurons release the neurotransmitter glutamate into surrounding tissue. High levels of glutamate overactivate receptors present on surrounding neurons, which kills the neurons (this is termed excitotoxicity). These dying neurons release their own stores of glutamate, leading to waves of dying neurons spreading out from the injury site. We aim to study how neurons respond to hypoxia using a genetic approach in the nematode C. elegans, which uses glutamate receptors similar to those in the human nervous system. The overactivation of these same receptors in C. elegans leads to excitotoxic neural death, and provides an excellent model system with which to study the process of neuronal injury. Preliminary results suggest that neurons try to respond to hypoxia by removing their glutamate receptors from the surface of the neuron. This is likely a protective response by the neurons to minimize damage after trauma; thus, modulating this response in the first hours after injury should protect nervous system function and minimize long-term damage. We have identified two new factors that mediate this response: the PHD protein EGL-9 and the PDZ protein LIN-10.

We propose experiments to determine the mechanism by which these two proteins function, and to determine whether they modulate excitotoxic death. Our proposal satisfies the goals of the NJCSCR in two ways. First, we will provide insight into the mechanism by which neurons respond to hypoxia, and identify agents that could block glutamate receptor activation and thus limit damage after traumatic injury. We will identify key targets for new therapeutic interventions that limit neuronal damage following spinal cord injury. Second, we will identify and characterize factors that regulate glutamate receptor function; these factors can be targeted to help strengthen synapses, thereby improving spinal cord function after injury. Researchers have previously used C. elegans to understand apoptotic cell death in humans; indeed, a Nobel Prize celebrated these achievements in 2002. Our 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 are likely to be applicable to human health.

Contact Information:
Eunchan Park, Ph.D.
Rutgers - Waksman Institute
190 Frelinghuysen Road
Piscataway, NJ 08854
eunchan@waksman.rutgers.edu
732-445-0954

Kurt Gibbs, Ph.D. – Principal Investigator
Rutgers, The State University of New Jersey - W.M. Keck Ctr. Collaborative Neuroscience
Grant Award: $150,000

Project Title: *The Effects of mir-133 on Functional Recovery after SCI*

There are several factors that inhibit recovery from spinal cord injury, ranging from failed regeneration of nerve fibers (axons) to an inflammatory immune response. Although some axons show signs of growth after injury, they collapse after encountering inhibitory signaling molecules from the surrounding environment that result from the injury. These molecules communicate through receptors on the surface of the axon to convey a signal that inhibits the axon's attempt to grow. Many of these inhibitory signals converge on a protein called Rho-A, which in turn relays this signal to other proteins that play a role in inhibiting axon regeneration and contribute to deleterious effects in other cells as well. It has been shown that preventing the activation of Rho-A results in increased functional recovery after spinal cord injury. Recent studies have revealed that cells use innate, small ribonucleic acid molecules, called microRNAs, to simultaneously modulate the levels of expression of many genes. In addition, it has been shown that the macrons, mir-133, can decrease the expression of Rho-A and the cell death-promoting protein, caspase-9.

In this study, we will assess the effect of increased expression of a synthetic version of mir-133 to decrease the expression of Rho-A and caspase-9 and its ability to improve functional recovery after spinal cord injury. We will also assess the administration of this treatment by lumbar puncture, as this mechanism offers a minimally invasive procedure to routinely deliver therapeutic agents in humans. This will be the first study to assess the effectiveness of mir-133 on improving functional outcome after spinal cord injury. This success of this work has the potential to provide a new therapy for spinal cord injury and pave the way for future studies that use multiple microRNAs for an increased therapeutic effect.

Contact Information:
Kurt Gibbs, Ph.D.
Rutgers – W.M. Keck Center
for Collaborative Neuroscience
604 Allison Road, Room D-251
Piscataway, NJ 08854
kurtmgibbs@gmail.com
732-445-2061