



**DIRECTORY OF GRANT AWARDS
2009 GRANT CYCLE**

**NEW JERSEY COMMISSION ON
SPINAL CORD RESEARCH**

2009 GRANT CYCLE

**DIRECTORY OF GRANT AWARDS
FOR SPINAL CORD INJURY AND
DISEASE RESEARCH**

JUNE 2009

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 2009 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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NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

MONICA DRISCOLL, Ph.D. – Principal Investigator

Grant Award - \$393,764

Rutgers - Molecular Biology & Biochemistry

Proposal Title: *Mechanisms of Neuronal Regeneration in a Genetic Model*

Spinal cord injury is a devastating event for victims and families. Tragically, we lack effective interventions that promote successful regeneration of injured neurons. A more detailed understanding of the molecular mechanisms of neuronal regeneration that act under physiological conditions will be required for design of novel and effective therapies.

Our lab studies molecular mechanisms of neuronal regeneration in the powerful experimental model system *Caenorhabditis elegans*. Key advantages of this system include the transparent body that allows us to use high power lasers to sever, and directly observe the regeneration of, axons within the living animal. Other amazing technologies enable us to measure localized calcium changes in regenerating neurons. At the same time, the model offers powerful genetic approaches such as the ability to conduct screens for new mutations that modulate neuronal regeneration.

In general, experiments that are implausible or impractical in higher organisms can be conducted rapidly, cheaply, and within physiological context in *C. elegans*. Since most basic biological processes, including cell death and axonal outgrowth, are conserved from nematodes to humans, we can identify critical molecules and decipher the basic molecular rules of a given process in the simple *C. elegans* and then use this information to address the function of related molecules in humans. The underlying working hypothesis of our research is that molecular elaboration of regeneration mechanisms in *C. elegans* will identify key molecules that can influence this process in humans.

We have identified a novel group of genes that influence early steps in neuronal regeneration consequent to axotomy in the living animal. Importantly, our data tie together previously unconnected observations in the vertebrate regeneration literature to suggest a conserved pathway for promoting new axon outgrowth in response to injury. We need to understand this pathway in more detail. The goals of our work will be to: 1) fill in cell biological details of what happens in regenerating neurons by tracking localized calcium changes, cytoskeletal changes and fluorescently tagged proteins, 2) figure out how each of the six regeneration gene defects change early regeneration events and determine the order in which the proteins encoded by these regeneration genes act, and 3) identify new genes that influence neuronal recovery from axotomy.

The experiments we plan should advance understanding of this regeneration process from the simple “listing” of six gene activities involved to a detailed temporal and mechanistic model for how these proteins act to promote regeneration. Because this pathway may be conserved between nematodes and humans, we expect our studies will advance understanding relevant to the challenging problem of post-injury neuronal repair and might ultimately suggest novel strategies for therapies in spinal cord injury.

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KIBUM LEE, Ph.D. – Principal Investigator

Grant Award - \$370,293

Rutgers - Chemistry & Chemical Biology

Proposal Title: *Inducing Motor Neurons by Combinatorial Signals for SCI*

Spinal cord injury (SCI), which mainly involves significant damage to motor neurons, affects about 12000-15000 Americans annually, 10000 people out of which experience life-long debilitating paralysis or even death due to the injury. Therefore, there is an urgent need for the development of cell-based therapies for the treatment of SCIs. In this regard, human embryonic stem cells (hESCs) are extremely promising resources for transplantation therapies as they possess the unique ability to self-renew and give rise to all somatic cell lineages.

Our goal is to identify and understand under what condition and how the cellular microenvironments of hESCs effectively differentiate into motor neurons for the treatment of SCIs. Although hESCs offer great opportunities by providing unlimited transplantable cell resources, controlling hESC differentiation into specific neurons (e.g. motor neurons) is the most important issue that needs to be addressed before their therapeutic applications for SCI can be fully realized.

Before developing innovative hESC-based clinical approaches, several obstacles such as preparing transplantable homogeneous neural cells, improving the ability to precisely control neural cell differentiation into specific neurons, and circumventing rejection issues by the immune system when stem cells are transplanted need to be surmounted. To address these challenges, a detailed insight into the functions of the extracellular microenvironments (environments surrounding the stem cells) and intrinsic cellular switches, which dynamically regulate hESC differentiation into neural precursor cells (NPCs) and motor neurons, must be studied. However, due to the presence of a plethora of signaling biomolecules within the hESC microenvironment, it is very challenging to study the role of hESC microenvironment in neuronal differentiation. Another significant challenge is to tune the intrinsic cellular regulators such as gene expression and signaling pathways. To manipulate gene expression within stem cells, small molecules, DNA, viruses, siRNA molecules have been used. Amongst these, RNA interference (RNAi)-mediated gene manipulation using small interfering-RNAs (siRNAs) is emerging and an important tool in stem cell biology. In this method, siRNAs are delivered to silence a target gene (stop gene expression) through specific destruction of that gene's mRNA. However, uptake of siRNAs by stem cells, especially hESCs, is very difficult. Therefore, there is an urgent demand for: i) innovative methods to evaluate multiple microenvironmental signals, and ii) improved methods to control the expression of key genes. Collectively, the proposed studies will establish new methods for selectively and efficiently generating human NPCs and motor neurons for therapeutic applications for spinal cord regeneration.

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MENGQING XIANG, Ph.D. – Principal Investigator

Grant Award - \$193,764

UMDNJ - Robert Wood Johnson Medical School

Proposal Title: *Role of Foxn4 in Spinal Neurogenesis and Gliogenesis*

Spinal cord injury is a devastating neurological injury that causes paralysis and neuropathic pain and for which there is as yet no effective treatment. Recent advances in stem cell research have brought closer to reality structural and functional regeneration of damaged spinal cords. Stem cell-based therapy aims to restore functional sensory and motor circuits and axon connections in the damaged spinal cord through stem cell transplantation or by activation of spared endogenous neural stem cells. Since stem cells can self-renew, are multipotent and can differentiate into many different types of neurons and glia, theoretically, they may promote functional recovery by regenerating neurons, reconstituting damaged circuits, and remyelinating axons. However, the injured adult spinal cord creates a rather poor micro-environment for cell survival, and for neuronal specification, differentiation and maturation. How to control the survival, proliferation and differentiation of transplanted or endogenous stem cells presents a major challenge for stem cell-mediated spinal cord repair. Thus, although stem cell-based therapy has been applied successfully in rodent models of spinal cord injury to restore limited sensory and motor functions, to develop this promising approach as a viable therapy, it is necessary to understand the developmental and genetic programs that direct the proliferation, specification and differentiation of neural stem cells.

Because differentiation of neural stem cells normally recapitulates the events that occur during embryogenesis, understanding the molecular basis of spinal cord development is a prerequisite for the future success of stem cell-mediated regeneration. Thus, this proposal aims to understand the molecular events that lead to the specification and differentiation of neuronal and glial cell types during spinal cord development. It will focus on the role of the Foxn4 forkhead/winged helix transcription factor in spinal gliogenesis and neurogenesis. Based on our previous work and preliminary studies, we have speculated that Foxn4 may be involved not only in neuronal specification, but also in determining glial cell fates and that Foxn4-expressing progenitors may give rise to both sensory interneurons and the astroglial lineage.

The proposed experiments are designed to test this hypothesis using molecular genetic approaches in the mouse and chicken model systems as well as to test the feasibility to achieve controlled generation of desired glial cells in the chick embryo. Together, these proposed studies are expected to provide important insights into the genetic regulatory network that underlies the determination and differentiation of various glial and neuronal cell types during spinal cord development, and in the long term, may help to identify novel molecular targets that can be used to promote reconstruction of functional neural circuits in the injured spinal cord.

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HEDONG LI, Ph.D. – Principal Investigator**Grant Award - \$392,830**

Rutgers - W.M. Keck Center for Collaborative Neuroscience

Proposal Title: *GABAergic Interneuronal Restricted Progenitors and Spinal Cord Injury*

Cellular transplantation has shown great promise in treating spinal cord injury (SCI). In animal models, acute transplantation of neural stem/progenitor cells (NSPC) improved motor functional recovery in SCI via neuroprotection, but this treatment has been found to be associated with increased hypersensitivity. In human patients with SCI, more than 50% develop sensory hypersensitivity, which greatly affects their quality of life. Loss of inhibitory interneurons after SCI is thought to be a major mechanism underlying this altered sensory function. Therefore, replenishing inhibitory interneurons by cell transplantation may be beneficial.

In this proposal, we address both motor and sensory malfunctions in SCI by acutely transplanting a recently identified GABAergic inhibitory interneuronal progenitor in contused rat spinal cords. Our hypothesis is that these neuronal restricted progenitor cells not only are neuroprotective upon acute transplantation, but also differentiate into inhibitory interneuronal phenotype that can reduce hypersensitivity. L2.2 and GE6 (GFP+) are novel clones of GABAergic interneuronal restricted NSPCs, which will provide the first opportunity to test their ability to improve motor function without hypersensitivity after acute transplantation. The outcome from this research will provide insights into the impact of this specialized progenitor in SCI that may have a dual effect on both motor and sensory functions. Once we show our proposal is effective, our future goal is to isolate equivalent human GABAergic progenitors from fetal tissues or embryonic stem cells and move towards cell-based clinical therapies for SCI and other diseases.

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WILLIAM WADSWORTH, Ph.D. – Principal Investigator**Grant Award - \$368,515**

UMDNJ - Robert Wood Johnson Medical School

Proposal Title: *Molecules Promoting Axon Guidance and Synaptogenesis*

Following injury, regenerating axons must be guided back to their targets in order for the proper connections of the nervous system to be reestablished. Several of the molecules that are involved in axon guidance were first discovered in the nematode *C. elegans*, a model organism that is extensively used for genetic analyses. Although the nervous system of this organism is relatively simple, the same molecules that function to ensure proper nervous system connections in the nematode also function to guide the building of more complex circuits in the human nervous system. It is known that these molecules are present at the sites of spinal cord injury and that they may have a profound influence on the ability of regenerating neurons to find their proper targets and form functional circuits. Using the powerful genetic techniques available in *C. elegans*, further molecules required for axon guidance and neural circuit formation are being discovered through genetic screens. Knowledge of these molecules and a better understanding of the mechanisms by which they function could lead to better treatments to regenerate normal neural connections following injury.

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FELLOWSHIP GRANT RECIPIENTS:

ABHISHEK PRASAD – Principal Investigator

Grant Award - \$60,000

New Jersey Institute for Technology

Proposal Title: *Spinal Cord Computer Interface for Command Signal Generation*

Spinal cord injury occurs as a result of trauma or disease. There are over 250,000 cases of SCI patients in USA alone, with approximately 11,000 new cases every year. During SCI, the descending fibers in the spinal cord (axons of the upper motor neuron) are damaged and therefore, they lose their connections with the lower motor neurons which control the skeletal muscles. If the injury is at the cervical level, it results in quadriplegia with little or no function remaining in the four limbs. In these individuals, there is a great need for voluntary command generation. A quadriplegic person can benefit from a voluntary command generation system in different ways. S/he can use this system to control her/his environment (like the control of a robot arm), gain self-mobility (wheelchair control), or have access to a computer to improve independence and quality of life. Alternative to the robot arm, the voluntary command signals can be used to activate the person's own paralyzed muscles via electrical stimulation.

The current brain-computer interface technique, which have been developed as a method of voluntary command generation suffers from some fundamental technical problems. As an alternative, in this project we are trying to record descending signals in the intact regions of the spinal cord above the point of injury to construct a neural interface for voluntary command generation. Such a neural interface is called a Spinal Cord Computer Interface (SCCI).

The feasibility and long-term stability of signals recorded from the rat spinal cord will be investigated in this study. Signals will be recorded from devices implanted in the spinal cord while the rats perform food reach-to-grasp task. Various statistical techniques will be used to demonstrate the information content of the neural signals. This study will also investigate the damage produced by the microelectrodes utilizing microscopy techniques and how that information can be used to modify the microelectrode arrays.

Another aspect of this study can potentially benefit the patients in rehabilitation. A quadriplegic individual with an implanted SCCI device will actively use the injured motor axons on a daily basis, which may well improve the preservation and sprouting of severed axons when combined with pharmacological therapies. Utilizing a multidisciplinary approach to treat SCI in future may help in improving a spinal cord injured individual's quality of life and it may also bring down the medical costs incurred by hospitals and rehabilitation centers.

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LAWRENCE SASSO – Principal Investigator

Grant Award - \$60,000

Rutgers - Biomedical Engineering

Proposal Title: *Continuous Microfluidic Analysis of CSF Inflammation Markers*

After a spinal cord injury, a variety of inflammatory signaling factors interfere with the regeneration of nerves across the injury site. Research has shown that cell damage caused by inflammation is one of the significant factors which interferes with nerve regeneration and recovery of sensation and muscle control. Unfortunately, the inflammatory response to spinal cord injury has not been well characterized. Due to this limitation, a precise therapeutic regimen has not been developed. The purpose of this project is to create diagnostics to continuously analyze the cerebrospinal fluid (CSF) from patients suffering from spinal cord injuries (SCI) for signs of inflammation. Since spinal cord inflammation following traumatic spinal cord injuries is correlated with secondary spinal cord damage and loss of sensory and motor function, the ability to better track inflammation markers will provide clinicians treating these injuries with more information about the progression of inflammation. This will enable new clinical studies into how specific therapies affect inflammation following SCI and how controlling inflammation improves patient recovery. It is hypothesized that by continuously monitoring the progression of inflammatory responses and their changes due to localized drug delivery regimens that true personalized treatment options may be developed to obtain the best prognosis possible for SCI patients.

A microimmuno assay device which continuously monitors the concentrations of these inflammatory markers sampled directly from patients' CSF has been designed and tested. The design is based on technology currently being developed where microscopic magnetic beads are used to measure inflammation markers. The beads are coated with an antibody to the inflammatory protein of interest and flow through specially designed microchannels where the inflammation markers can bind to their surfaces. When there is a higher concentration of a marker present, more of it is attached to each bead as it reaches the end of the channel. Fluorescent molecules then attach to the inflammation markers on the beads, and the concentration of the inflammatory marker is measured by quantifying how brightly the beads fluoresce.

The device will first be tested on rats to ensure that it can monitor inflammation in a live animal for extended periods of time. After the device is shown to have good correlation to standard immunoassays, it will be tested with archived, de-identified samples of CSF from SCI patient. This testing will ensure that the device can give reliable results in a clinical setting. When this technology is used by clinicians on patients with recent injuries, the detailed CSF inflammation data from the device will assist in the development of new treatments and administration of personalized therapies. These therapies will reduce the negative effects of inflammation on nerve regeneration, helping to improve the prognoses for spinal cord injury patients.

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HAICHANG LI, Ph.D. – Principal Investigator

Grant Award - \$100,000

UMDNJ – Robert Wood Johnson Medical School

Proposal Title: *Molecular Mechanisms of Axon Outgrowth and Guidance*

Spinal Cord Injury (SCI) is one of the most devastating neurological injuries affecting millions of people worldwide. More than 255,000 persons in the United States are alive with SCI in 2007 (<http://www.spinalcord.uab.edu/>), and the cost of managing the care of SCI patients approaches \$ 4 billion each year. These injuries cause damage to the motor axons (that control movement) and sensory axons resulting in paralysis or loss senses. Currently, one strategy for SCI repair is to promote axon outgrowth to make proper connections that can compensate for the functional loss due to injury.

The research in Wadsworth lab is studying the molecular mechanism of UNC-6/netrin-dependent axon outgrowth and guidance in *C. elegans*. We use *C. elegans* as a model because they can be easily manipulated by powerful genetics and can also serve as an excellent model to study axon regeneration in vivo. Actually, most guidance molecules involved in the development of the human nervous system, were first discovered in *C. elegans*. Recent studies show that netrin and their receptors persist and their expression are dramatically changed at the sites of spinal cord injury, which could have a profound influence on the ability of regenerating neurons and axons to form functional circuits. Netrin-1 is an important regulator for the outgrowth and migration of embryonic stem (ES)-derived neurons that may provide a useful tool to replace damaged neurons after injury. We have identified 2 new genes that regulate UNC-6/netrin-dependant axon outgrowth and guidance signaling: rpm-1 and clec-38. These genes negatively regulate the activity of guidance receptors and are also required for presynaptic development. Our research provides an excellent model to study the regulation of guidance receptor to control axon outgrowth and guidance and make functional connections after injury.

The goal of this proposal is to further understand the molecular mechanism of axon outgrowth and guidance. Here, I proposed to continue my study on the function of RPM-1 and characterize another novel conserved, neuronal protein UNC-80, which we have identified recently. The proposed research will determine how RPM-1 affects the axon guidance receptors and regulate the axon guidance and outgrowth to make the appropriate connections, and how UNC-80 functions in UNC-6/netrin-dependant axon outgrowth and guidance signaling. Detailed characterization of these molecules and a better understanding of the molecular mechanism of axon outgrowth and circuit formation will contribute to address the similar process in human, which will be beneficial towards development of new therapies to help to repair damaged spinal cord.

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OMAR HASAN – Principal Investigator

Grant Award - \$60,000

UMDNJ - Robert Wood Johnson Medical School

Proposal Title: *Elucidating the Interplay between Inhibitory Factors Preventing Axon Regeneration in CNS Injury*

There are many factors preventing the spinal cord from regenerating itself after injury. Evolution has not been kind to man in this regard and in a sense has made it unfavorable for regrowth after such a devastating injury. However, over the past 100 years we have been able to decipher many of the mechanisms that the body has developed over time to prevent regrowth of the spinal cord after injury. In this project we intend to exploit this knowledge. We will combine several recent advances into one tool in order to look at some of these mechanisms in the hope of understanding them in order to develop pharmacological therapies that might one day enable spinal cord regrowth. One group of these mechanisms involves proteins made by the body in development to help the nervous system grow, but in a controlled way. However, in the adult this becomes a problem, because although these facilitate axon growth when we are in the womb, they prevent regrowth of the nerves composing the spinal cord after a spinal cord injury. It is these proteins we hope to learn about and hopefully block their effect in preventing recovery from spinal cord injury. We will specifically eliminate the function of three proteins simultaneously and expect to facilitate axon regrowth more than eliminating only one of them does.

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