DIRECTORY OF GRANT AWARDS
2006 A GRANT CYCLE

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

2006 A CYCLE

DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

JUNE 2006

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 2006 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 PO Box 360, Health & Agriculture Building, Market and Warren Streets, 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:

PRINCIPAL INVESTIGATOR – **SALLY MEINERS, PH.D.**
Basic Science Proposal
Grant Award – $315,462

Proposal Title**: Engineering Nanofibrillar Surfaces for Spinal Cord Repair**

Thousands of new cases of spinal cord injury occur each year in the USA alone. However, despite recent advances, there is at present no cure for the resulting paraplegia or quadriplegia. The goal of the proposal is to attempt to repair spinal cord injuries by implanting into the lesion a prosthetic composed of nanofibers so as to provide a bridge across the lesion for regenerating axons. In addition to unmodified nanofibers, we will also employ nanofibers whose surfaces are modified with a bioactive peptide. This peptide, derived from a sequence within the neuro-regulatory molecule tenascin-C, has been demonstrated in vitro to increase axonal growth from spinal cord motor and sensory neurons. Preliminary data suggest that an implant of polyamide nanofibers permits axonal growth following spinal cord injury, and that this ability greatly increases with the addition of the tenascin-C peptide. Moreover, because neurites extend along the nanofiber axis, the proposed work will utilize nanofibrillar implants that incorporate nanofibers deposited in an aligned array. In other experiments, implantation of nanofibers into the injured spinal cord resulted in reduced levels of scar-associated molecules and the pro-inflammatory cytokine interleukin-1beta.

As such, the specific aims of this work are directed toward exploring the utility of peptide-modified nanofibers as a multi-faceted approach to spinal cord injury. These matrices can potentially encourage regeneration by a) encouraging axon outgrowth; b) providing a permissive directional cue; and c) decreasing inhibitory cues in the lesion environment. We believe that the success of our research program will validate a strategic approach to extend this research to larger animals and to pre-existing spinal cord injuries, and to investigate the mechanism by which nanofibers attenuate the inflammatory cascade. This will be the first use of nanofiber technology in therapies designed to treat spinal cord injury.

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PRINCIPAL INVESTIGATOR – **HAESUN A. KIM, PH.D.**
Basic Science Proposal
Grant Award – $397,066

Proposal Title**: Functional Analysis of erbB2 Signaling During Myelination**

Experimental transplantation has provided overwhelming proof for the potential of repairing damaged nerves by transplanted myelinating-forming cells. Schwann cells, the myelin-forming cells of the peripheral nervous system (PNS), are good candidates for such therapy. Schwann cells grafted at a nerve lesion secrete factors that promote survival and regeneration of the injured neurons. Schwann cells also improve nerve conduction by re-building myelin segments on regenerating axons, a process essential for the normal functioning of nerves. Most important, Schwann cells can be easily isolated from the patient's peripheral nerves, expanded in culture and grafted in the CNS lesions. However, despite the repair functions, the number of myelinated nerves following Schwann cell transplantation in the lesions remains insufficient. Therefore, modifying Schwann cells to enhance their abilities to form myelin could be one strategy to improve their nerve repair functions in the CNS lesions. In order to put such therapeutic strategy into practice, it is important to understand molecular mechanisms that regulate Schwann cell myelination. It has been shown recently that a growth factor called neuregulin promotes myelination by binding to the Schwann cell surface receptor, erbB2, and activating it. ErbB2 activation then generates intracellular signals that initiate Schwann cell myelination. Therefore, developing an experimental strategy to enhance erbB2 signals in transplanted Schwann cells might provide a therapeutic benefit to restore nerve functions following spinal cord injury.

The objective of the proposed study is to determine the therapeutic potential. This will be done by: i) defining molecular mechanisms that regulate Schwann cell myelination, ii) determining effects of enhanced erbB2 signaling during myelination, and iii) determining whether the enhanced erbB2 signaling in transplanted Schwann cells could improve myelination of regenerating neurons. An innovative system for culturing myelinated neurons will be used for the study. In the system, cultured myelinated neurons can be injured and subsequently allowed to regenerate and be remyelinated by Schwann cells. A combination of genetic and biochemical strategies will be used to define the erbB2 signaling mechanisms that promote myelination. We will also modify Schwann cells to express "synthetic erbB2 proteins" that are activated by a pharmacologic drug, but not by neuregulin, and therefore generate extra erbB2 signals within the Schwann cells. The Schwann cells will then be used to determine whether the enhanced erbB2 signals can improve myelination of regenerating neurons.

Altogether, the present study will define molecular mechanisms involved in regulating Schwann cell myelination and also provide insights into developing a therapeutic strategy for improving nerve repair functions of transplanted Schwann cells in spinal cord lesions.

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FELLOWSHIP GRANT RECIPIENTS:

PRINCIPAL INVESTIGATOR – **WENYING ZHANG, M.D., M.S.**
Graduate Fellowship
Grant Award – $60,000

Proposal Title: **Identifying and Characterizing Novel Genes that Protect Against Neuronal Necrosis In Vivo**

Neuronal necrosis initiated by ion channel hyperactivation plays a major role in both the initial and prolonged death of neurons consequent to SCI. Necrosis induced by injury occurs in two phases - the first due to the physical injury, and the second wave of death induced by the necrosis of the neurons directly injured. Since it has been suggested that saving function of as little as 10% of spinal cord neurons would restore locomotion, it is clear that blocking/delaying secondary neuronal necrosis would significantly limit incapacitating neuronal loss. Regrettably, the development of effective neuroprotective therapies has been hampered by incomplete understanding of the molecular mechanisms of necrosis.

A central goal of my work is the identification of genes protecting against necrosis induced by ion channel-inflicted neuronal injury. I use the nematode C. elegans, which has been fundamental in deciphering mechanisms of another type of death called apoptosis (see 2002 Nobel Prize in Physiology and Medicine). Since most basic biological processes, including injury-induced neurodegeneration, are conserved from nematodes to humans, we can exploit uniquely applied genetic approaches in the C. elegans model system to identify critical molecules and decipher the basic molecular rules of channel-induced necrosis. This information can then direct studies that address the function of related molecules (homologs) in humans and suggest novel targets for therapeutic interventions for spinal cord injury. Our underlying working hypothesis is that molecular elaboration of necrosis mechanisms in C. elegans will identify key molecules protecting against necrosis in humans. Manipulating the identified genes/proteins is a plausible strategy for blocking the devastating 2^{o} necrosis that follows initial injury. I have conducted the first forward genetic screen for novel genes that can mutate to enhance neuronal necrosis. Since the mutant version enhances necrosis, the normal (wild type) function of the identified genes should actually be neuroprotective. My first aim is to molecularly clone at least two loci that can mutate to enhance necrosis. I will precisely position these 2 necrosis enhancer genes on the genetic map, molecularly identify the enhancer genes and describe the death-enhancing mutations. My second aim is to determine the molecular mechanisms of action of these necrosis enhancers. I will characterize properties of 2 necrosis enhancer genes, determine where these genes act in the genetic pathway for necrosis, and determine if these genes have a mammalian counterpart potentially involved in necrosis and spinal cord injury. This work is important because we will identify novel molecules that contribute in significant ways to prevent the necrosis that accompanies injury. Since the molecules identified are likely to be similar in nematodes and humans, identification of such necrosis genes has clear therapeutic potential.

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PRINCIPAL INVESTIGATOR – **JIANZHONG HAN, PH.D.**
Postdoctoral Fellowship
Grant Award – $100,000

Proposal Title: **Signal Transduction in Myelin Inhibition of Axonal Growth**

Spinal cord injury (SCI) is one of the most devastating neurological injuries affecting millions of people worldwide. Normally, nerve fiber regeneration at the lesion site is very limited, which is partly due to the presence of axon growth inhibitors in the ambience. To date, three myelin-derived proteins, namely MAG, Nogo A, and OMgp, are found to be the major source of inhibition. Significant progress has been made in identifying the receptor and coreceptors for these myelin inhibitors over the past several years. However, the intracellular signaling mechanisms underlying the inhibitory activities of these myelin molecules remain largely unclear.

In this proposed study, we will use primary neuronal cultures to investigate the signal transduction mechanisms underlying axon inhibition by three myelin-associated proteins. The use of cell culture provides the advantages for chemical and molecular manipulations. The study is based on our previous work that protein phosphatases, calcineurin and PP1, are critical in mediating Ca2+-dependent axon repulsion. I have already obtained some preliminary data to demonstrate that axon repulsion induced by MAG could be blocked if this phosphatase cascade was disrupted. Since axon repulsion represents one of the three inhibitory responses of regenerating axons, we are to further test this hypothesis and extend our work to mammalian CNS axons in the first aim of the this study. Moreover, previous studies have established that myelin inhibition can be overcome by elevation of cyclic AMP, an important second messenger for neuronal functions. This finding was originally obtained in cell culture and has been used to promote axon regeneration in adult spinal cord. However, it is still not clear how cAMP elevation leads to enhanced axonal growth in the presence of myelin molecules. We have identified an important mediator called inhibitor-1 in cAMP regulation of axonal growth. I-1 is also the key molecule in calcineurin-PP1 cascade. So it is natural to wonder if the antagonistic effect of cAMP relies on phosphatase cascade inhibition. We will test this notion in our second aim of his project.

Overall, we will utilize primary neuronal cultures to dissect signaling steps that lead to axon inhibition by myelin components. We hope that we can obtain a much better understanding of how myelin inhibit axonal fibers, which could form the foundation for enhancing regeneration of injured nerve fibers in spinal cord. Specifically, the knowledge gained from this project will help to identify novel molecular targets that can be used for drug development or gene therapy in the clinical treatment of SCI.

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PRINCIPAL INVESTIGATOR **– SAUMYA PANT**
Graduate Fellowship
Grant Award – $60,000

Proposal Title: **Rab-10 and its Effectors in Glutamate Receptor Recycling**

Spinal cord injury causes nervous system damage by a variety of means. Mechanical damage at the initial injury site causes release of intracellular contents, for example neurotransmitters, and also often leads to localized loss of oxygen. Loss of oxygen leads to ATP depletion, depolarization, and further release of neurotransmitters including large quantities of glutamate. The excess glutamate then signals further depolarization in surrounding cells creating a viscous cycle that can ultimately lead to excitotoxic cell death.

Preventing such expansion of the injury could greatly reduce loss of spinal cord function. An important means of regulating glutamate response is the regulation of trafficking of glutamate receptors - either preventing or allowing receptors to reach the cell surface. Our lab utilizes C elegans to dissect the process of glutamate receptor function, particularly its movement from internal vesicles where it is inactive to the plasma membrane where it is active. We established that rab-10 regulates access of glutamate receptors to the plasma membrane in vivo. We now seek to better understand the molecular mechanisms that regulate this glutamate receptor movement, so that new therapies controlling this process can be developed.

Our approach to this problem will include elucidating the role of rab-10 and its effectors in glutamate receptor recycling and also directly testing the effects of reduced glutamate receptor transport as a means of reducing spinal cord damage.

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PRINCIPAL INVESTIGATOR **– ZHAOXIA QU**
Graduate Fellowship
Grant Award – $60,000

Proposal Title: **Mechanism of Erythropoietin Effects on Neural Stem Cells**

Thousands of New Jersey patients suffer from spinal cord injury, which is currently a devastating disease due to the very limited regenerative ability of the central nervous system. Recent studies including ours indicate that Erythropoietin (EPO), a growth factor that has long been known to stimulate red blood cell production, improves recovery after spinal cord injury and other types of central nervous system injury in animals. The mechanisms by which EPO stimulates recovery and tissue repair are not well understood. We recently discovered that neural stem cells express EPO receptors. In addition, preliminary studies in our laboratory indicate that EPO activates a typical cell survival and proliferation pathway in neural stem cells. Furthermore, we found that EPO significantly enhanced the expression up-regulation of nestin, a neural stem cell marker, in injured rat spinal cords.

We hypothesize that EPO promotes neural stem cell survival, proliferation, and/or differentiation in the central nervous system. We propose to determine the mechanisms by which EPO protects neural stem cells and stimulates neural stem cell proliferation and differentiation in vitro and in injured spinal cord. EPO is an attractive therapeutic candidate because it is used clinically and even in patients with spinal cord injury to treat anemia. Thus, its safety is well established. Johnson & Johnson is interested in initiating clinical trials to evaluate the effects of EPO on spinal cord injury. These proposed studies should not only provide a strong rationale for testing EPO treatment in a clinical trial of spinal cord injury or some other central nervous system disorders, but should also provide important insight into the normal physiological function of EPO in the central nervous system. Moreover, although neural stem cells exist in the adult central nervous system, the regenerative ability of adult central nervous system is still limited, and stem cell transplantation have not yielded dramatic improvements in function and regeneration. EPO may provide a means of stimulating endogenous neural stem cells to protect and perhaps promote recovery of function. Studies on how EPO affects survival, proliferation and differentiation of neural stem cells should provide insights into the mechanisms that promote neural stem cell participation in the repair and recovery of function after spinal cord injury, and may help to improve stem cell transplantation therapies.

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PRINCIPAL INVESTIGATOR **– JORGE L. DAVILA**
Graduate Fellowship
Grant Award – $60,000

Proposal Title: **miRNA Targets Regulating Stem Cell Differentiation**

There are over 250,000 spinal cord injured individuals living in the US. This staggering number reflects the urgency to find a cure for this condition. Recently, stem cell transplantation therapy has become an enticing therapeutic option for spinal cord injured patients. A major limiting factor to utilizing stem cells as a feasible treatment for spinal cord injury is the uncertainty of the fate of these cells once transplanted. Stem cells, once transplanted, have the ability to differentiate into a wide range of cell types or to continue to proliferate without differentiating into a mature phenotype. To adapt neural stem cells for therapies, we must understand more of their internal cell mechanisms and programming, as well as their interactions with host tissues, which will lead to methods stabilizing restricted differentiation or promoting differentiation towards desired phenotypes.

In this proposal we intend to identify key regulators of neural stem cell (NSC) differentiation to advance protocols for NSC transplantation. Recent studies have begun to clarify molecular interactions involving genes that promote differentiation of NSCs towards specific phenotypes. MicroRNAs (miRNA) are a novel class of gene linked to the regulation of gene function. Studies have associated several of these miRNAs with cell differentiation and other developmental processes, suggesting that they might be master regulators of protein expression. We intend to find specific regulators of NSC differentiation which are regulated by unique miRNAs by a series of biochemical and bioinformatics approaches. Thus, we believe that by identifying genes related to this form of regulation it will be possible to elucidate NSC differentiation mechanisms, which will provide novel approaches to regulate NSC fates. The ability to control the fate of NSCs may lead to optimized therapeutic NSC transplantation protocols for spinal cord injury patients.

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PRINCIPAL INVESTIGATOR **– LULU LI**
Graduate Fellowship
Grant Award – $30,000

Proposal Title: **Electric Stimulation of Neural Differentiation from Embryonic Stem Cells**

There are 450,000 people who live with spinal cord injury in the United States, and the figure increases by 8,000 each year. Recovery in individuals with spinal cord injury is hindered by the limited ability to regenerate healthy nerve cells and reestablish functional neural connections by the central nervous system. Neural transplantation studies in humans require a reliable source of implantable nerve cells.

This challenge has partially been addressed by investigating the propagation of embryonic stem cells. Embryonic stem cells can be cultured in vitro in an undifferentiated state infinitely while still remaining highly pluripotent. They are capable of forming all types of cell lineages including nerve cells. However, the derivation of embryonic stem cells is complicated by many factors. Several differentiation strategies have been developed to induce embryonic stem cell differentiation into neuronal cells and support glia cells using growth factors and conditioned media.

Nevertheless, one factor that is not well understood is the electrical environment. Electromagnetic field of significant field strength has been demonstrated to occur at early stage of embryonic development in various species. These non-invasive fields have been successfully applied to enhance nerve regeneration and promote axon elongation, both in vitro and in vivo, of various types of cells.

Therefore, the proposed study will construct a differentiation system that integrates with an applied electromagnetic field. It will be used to examine and optimize the charge effects on embryonic stem cell differentiation into nerve cells. This approach may serve as an effective and safe therapeutic method for promoting nerve regeneration after spinal cord injury.

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PRINCIPAL INVESTIGATOR **– HSIAO-WEN LIN**
Graduate Fellowship
Grant Award – $60,000

Proposal Title: **Anti-Inflammatory Effects of CNTF on Microglia**

Recovery of motor functions is the ultimate goal of treatments for spinal cord injury (SCI) and diseases of the spinal cord. However, functional recovery often is limited as a result of inflammation within the spinal cord that contributes to the loss of neurons and their support cells as well as the production of growth inhibiting molecules. The cytokine, ciliary neurotrophic factor (CNTF) has been found to have dramatic neuroprotective effects. It is produced in the major support cells of the nervous system, astrocytes, and following SCI its production is rapidly increased. Administering CNTF to animals with SCI can decrease the loss of neurons, increase the regrowth of their processes and enhance the recovery of motor functions. CNTF also delays the onset of motor symptoms in multiple sclerosis and experimental autoimmune encephalomyelitis (EAE), an animal model of the disease. It is conceivable that CNTF accomplishes its protective effects by depressing the immune responses in SCI and MS. This is our hypothesis.

Our research aims to understand how CNTF affects the resident immune cells of the nervous system, microglia. Our preliminary data show that CNTF decreases the immune functions of microglia. It does so by depressing the ability of microglia to trigger other immune cell reactions. It prevents microglia from chewing up cells and nearby processes, thus limiting the extent of tissue damage. Our research has shown that it stimulates the production of signals that can promote the survival of spinal cord motor neurons. Based on these findings, I propose to continue to investigate the effects of CNTF on the immune functions of microglia under this fellowship. I will examine whether CNTF affects the direct interaction between microglia and immune cells and whether it alters the ability of microglia to attack myelin, which is the insulation that surrounds nerves.

Further research on the effects of CNTF on microglia will benefit spinal cord research in two ways. First, it extends our knowledge on how CNTF as a cytokine can reduce the severity of SCI and diseases that affect the spinal cord. Second, our research may support the use of CNTF in therapeutic strategies for SCI or diseases that affect the spinal cord. Thus, our studies match one of the major research areas funded by NJCSCR, "developing strategies to prevent or treat secondary complications arising from injury or disease to the spinal cord."

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PRINCIPAL INVESTIGATOR **– KELLY C. KRANTZ**
Graduate Fellowship
Grant Award – $60,000

Proposal Title: **Investigating the Mechanism of Clathrin Uncoating, A Key Step in Synaptic Transmission**

The mammalian spinal cord is made up of cells called neurons, which form a network that allows signals to pass between the spinal cord and other areas of the body. These signals can be messages from the brain telling the body to react, or the body telling the brain that something is wrong. If the network of neurons in the spinal cord becomes damaged and can no longer transmit signals, paralysis often occurs. In order to restore signal transmission after spinal cord damage we first have to understand how the signals are transmitted in healthy neurons. It is known that the signal that passes between neurons is tiny molecules. Inside a neuron these molecules are packaged in vesicles. The vesicles are fragments of the membrane encasing all compartments within the neuron that form a bubble around the signal molecules. The vesicle is then transported to the end of the neuron where it fuses with the neuronal membrane, which is the membrane surrounding the entire neuron. This releases the signaling molecules into the space between neurons, the synapse, where they travel to and enter a neighboring neuron. In order for more signal to be sent the vesicle membrane that is now part of the neuronal membrane has to be brought back into the cell and transported to an internal compartment where it can be reused to package more signaling molecules. This process known as synaptic vesicle recycling is when a vesicle forms at the neuronal membrane and is transported back to a compartment inside the neuron. Synaptic vesicle recycling is not fully understood and our research focuses on increasing our understanding this process.

Previous research has shown that vesicles form when a coat protein, a special class of proteins that help form vesicles, forms a layer over the membrane and mechanically deforms them membrane into a vesicle. In synaptic vesicle recycling clathrin is the major coat protein. The coating process results in a vesicle surrounded by a layer of coat protein. In order for this vesicle to fuse with its target membrane the coat protein has to be removed so that the machinery in the vesicle membrane that helps it fuse with the target membrane can get close enough to the target membrane. The proteins that remove the clathrin coat are Hsc70 and auxilin. Unfortunately, nobody knows how Hsc70 and auxilin remove the clathrin coat. In order to expand our understanding of this process I aim to purify Hsc70, auxilin and fluorescently tagged clathrin coated vesicles, and then set up an uncoating reaction outside the cell. Since, the reaction will be taking place outside cell I will be able to monitor the progress of the reaction over time by looking at changes in fluorescent signal coming from the proteins which make up the clathrin coat. This system will allow me to determine the biochemical mechanism Hsc70 and auxilin are using to uncoat clathrin coated vesicles. Determining this mechanism will increase our understanding of synaptic vesicle.

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PRINCIPAL INVESTIGATOR **– NRIPEN SHARMA**
Graduate Fellowship
Grant Award – $60,000

Proposal Title: **Metabolic Engineering of Stem Cell Differentiation into Oligodendrocytes**

Spinal cord injuries (SCI) due to accidents, sports or violence are a major cause of physical disability in varied age groups of the affected residents of New Jersey. One of the secondary effects of these injuries is the loss of an insulating sheath called myelin around nerve fibers with inability of a particular cell type of the central nervous system called oligodendrocytes to produce myelin. There are no thorough approaches to improve function of these cells at the injury site except for transplantation of immature cells capable of producing myelin obtained from various sources. Difficulty in isolation and obtaining large numbers, inhibitory effects from other cell types and lack of proper myelin formation are some of the problems associated with this approach.

Recently, the effect of the biochemical environment for myelin synthesis as compared to the inherent properties of the transplanted cells is gaining more attention. Since the main function of oligodendrocytes is to produce myelin, a lipid rich membrane, our proposed research is focused on understanding the biochemical factors that lead to myelin synthesis. We envisage using the concept of metabolic engineering to perform a systematic characterization of the biochemical factors responsible for myelin production. The generalized application of metabolic engineering is not limited to biochemical system characterization but also utilization of the same to produce more efficient products or boost function.

In order to perform these studies, we shall utilize embryonic stem cells that can serve as an excellent starting source. These cells can grow indefinitely in culture, can produce unlimited number of myelin producing cells and have the unique property to be amenable to genetic and biochemical manipulations. In this regard, the potential of embryonic stem cells to generate any cell type in the body can be exploited in a controlled environment as a solution to the problem. The long term goal of this research is to identify and further utilize key supplementation regimens during embryonic stem cell differentiation studies to remyelinate axons in vivo.

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PRINCIPAL INVESTIGATOR **– JIAN CHEN, PH.D.**
Postdoctoral Fellowship
Grant Award – $100,000

Proposal Title: **Adeno-Associated Virus-Mediated Expression of Cell Adhesion Molecule L1 Improves Axonal Regrowth & Functional Recovery after Compression Spinal Cord Injury in Adult Mice**

Neural cell adhesion molecules have been shown to be able to promote neuronal survival and neurite outgrowth. Among them, L1 promotes neurite elongation on axons and Schwann cells by a homophilic binding mechanism in trans-interaction that is between the cell surface of the neighboring and interacting partner cells, for instance Schwann cell and neuron, or axon and axon.

L1 is upregulated by neurons and Schwann cells after a peripheral nerve lesion and has been implicated in the successful axonal regeneration in the peripheral nervous system. The regeneration inhibitory glial cells in the central nervous system do not express L1. L1 has been shown to be able to overcome inhibitory cues for neurite outgrowth in vitro and in vivo and to promote recovery of locomotion in a rat spinal cord and optic nerve lesion paradigm when applied transiently to the lesion site. Together with the growth associated protein GAP43 it allows cerebellar Purkinje cells to regenerate their axons. Although L1 is abundantly expressed in the central nervous system during spinal cord development, its expression declines to undetectable levels in adult mammals. Even after spinal cord injury that induces several developmental cell fate determinants, L1 is not upregulated in expression.

On the other hand, adult zebrafish achieves successful axonal regeneration and functional recovery after spinal cord transection: Axonal regrowth and functional recovery are eliminated when L1 expression is blocked. To convey neurite outgrowth conducive properties for therapy in the non-permissive environment of the adult mammalian spinal cord, we propose to express L1 at the lesion site of the compression-injured adult mouse spinal cord via an adeno-associated viral vector system and investigate whether severed axons and neurons are able to restore functional connections as measured by histological anterograde and retrograde tracing and by videotaped quantitative assessment of locomotor parameters. We wish to thus contribute to the strategies designed to positively overcome the largely inhibitory environment in a mouse model of spinal cord regeneration.

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