DIRECTORY OF GRANT AWARDS
2007 A GRANT CYCLE

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

2007 A CYCLE

DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

JUNE 2007

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 2007 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 – Bonnie L. Firestein, Ph.D.

Rutgers, The State University of NJ
Department of Cell Biology & Neuroscience
Basic Science Proposal
Grant Award - $366,865

Proposal Title: Astroglial of EAAT-1 in Spinal Cord Neuroportection

During spinal cord injury, cells in the spinal cord are mechanically damaged due to the trauma of injury. A bit later, the cells are further damaged by a chemical called glutamate, which is released at high levels around the injury site.

Our project tries to reduce the toxic effects of glutamate. Previous studies in our laboratory show that supporting cells, called astroglia, that are present in spinal cord play a role in protecting neurons from glutamate-induced damage. In fact, the astroglial cells produce a protein called EAAT-1 that helps to remove glutamate from the area surrounding the neuron. Thus, production of EAAT-1 can block glutamate damage. Based on our preliminary data, we hypothesize that when astroglia produce extremely high levels of EAAT-1, neurons will be protected from glutamate released when the spinal cord is injured.

We will test our hypothesis with two sets of experiments. First, we are going to use genetic manipulation to produce astroglial cells that have high levels of EAAT-1. We will then test whether these cells can protect spinal cord cells that are grown in a dish. We will then move to a system that is more relevant to SCI in humans. We will inject the genetically altered cells into rats with spinal cord injury. We will examine whether the injection of these cells increases the mobility and function of these rats. Thus, the results of our studies will identify whether transplantation of astrocytes with high levels of EAAT-1 may be a viable option for treatment of patients with spinal cord injury.

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PRINCIPAL INVESTIGATOR – Jonathan Eggenschwiler, Ph.D.

Princeton University
Department of Molecular Biology
Basic Science Proposal
Grant Award - $360,400

Proposal Title: Shh Signaling and Neuronal Differentiation of ES Cells

Damage to the spinal cord resulting from trauma or disease severely disrupts the quality of life and livelihoods of some 6,000 New Jersey residents (over a quarter of a million nationwide). Not only does spinal cord injury (SCI) leave its devastating mark those who suffer from it as well as their families, its economic impact is substantial. For these reasons, finding therapies to permanently restore spinal cord function in patients is a major goal of many neurologists and neuroscientists today.

The generation and manipulation of human Embryonic Stem (ES) cell lines holds great promise for transplantation-based therapy of SCI. The hope of those working in the field is that by directing ES cells to become specific types of neurons in a tissue culture dish, we can have a renewable source of precisely those cells that are damaged by SCI. These cells would then be reintroduced by transplantation into the damaged are of the spinal cord allowing connectivity, and thus function, to be restored. Indeed, transplantation of ES cell-derived neurons or glial (support) cells has shown considerable restoration of function in animal models for spinal cord injury.

Nevertheless, restoring more substantial spinal cord function will ultimately rely on our ability to generate the entire repertoire of neuronal and glial cell types damaged by SCI. Although methods allowing for generation of all of these cell types are being developed, we need ways to control the generation with better resolution. To this end, we are conducting basic research to understand how a particular process by which cells communicate with one another, called “Shh signaling”, guides the identity of neurons and glia generated from ES cells. Although our laboratory uses mouse ES cells as a model because they can be easily manipulated by genetic techniques, we plan to extend our analysis to human and non-human primate ES cells. Our work centers on a recent discovery that a structure on most mammalian cell types, called the primary cilium, plays a key role in the Shh signaling process. By studying when and how the primary cilium is generated as ES cells become neurons, and more specifically, how the primary cilium is used to convey Shh signals, we hope that we may manipulate this signaling process precisely to produce large numbers of cells of any given variety for use in transplantation-based therapies.

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PRINCIPAL INVESTIGATOR – Yi Ren, Ph.D.

Rutgers, The State University of NJ
W.M. Keck Center for Collaborative Neuroscience
Basic Science Proposal
Grant Award - $398,602

Proposal Title: The Role of Macrophage Migration Inhibitory Factor in Spinal Cord Injury

Macrophage migration inhibitory factor (MIF) has been linked to fundamental processes such as amplification of inflammatory and immune responses and stimulation of cell growth. MIF is rapidly released from pituitary and monocyte/macrophage in response to infection and stress and then stimulates the production of pro-inflammatory mediators. It has been shown that these increased mediators not only contribute to the amplification of inflammatory responses but also inhibit neuronal growth. The very unique properties of MIF are that its expression is stimulated by glucocorticoids and it overcomes the anti-inflammatory effects of glucocorticoids. Furthermore, MIF can cause neuron death directly in spinal cord injury. MIF deficient mice develop normally, but are extremely resistant to septic shock lethality and diminish production of pro-inflammatory mediators upon challenge with bacterial endotoxin. These results clearly demonstrate how a single gene could play no detectable role during normal growth, suddenly become critical in the setting of a pathologic challenge. These results also reveal that inhibition of MIF may pose little threat under normal circumstances, but provide a powerful intervention in the setting of a systemic inflammatory response.

Our preliminary data showed that MIF was up-regulated after spinal cord injury (SCI). Therefore, we will first investigate whether increased MIF in injured spinal cord would activates astrocytes and microglia cells, which are two major types of resident cells in spinal cord participating inflammation. Activation of these cells is believed to play crucial roles in the failure to neuronal regeneration after SCI. Given the property that MIF deficiency is associated with significant inhibition of inflammatory responses, we will examine whether MIF deficiency would impair the inflammatory responses in SCI by using MIF deficient mice received SCI.

Finally, we will explore whether targeting MIF would enhance the anti-inflammatory effect of methylprednisolone (MP) and improve functional recovery in SCI.

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PRINCIPAL INVESTIGATOR – Ronald P. Hart, Ph.D.

Rutgers, The State University of NJ
W.M. Keck Center for Collaborative Neuroscience
Basic Science Proposal
Grant Award - $117,883

Proposal Title: Overcoming Myelin Inhibition with MicroRNA's

The goal of our project is to develop small RNA molecules ("microRNAs") that can be used therapeutically to enhance regenerative growth after spinal cord injury.

Our collaborator, Dr. Marie Filbin of Hunter College, developed a technique using cultured cells to reproduce the inhibition of neuronal growth similar to that found in injured spinal cord. Her work showed that specific cell signals, such as cyclic AMP (cAMP), can reverse the blocking of growth caused by several different inhibitory proteins found in injured spinal cord. There is now new evidence that this process requires the synthesis of proteins in the extended region of a neuron called a neurite. Since microRNAs are known to regulate synthesis of new proteins, we reasoned that cAMP may affect neurite growth by controlling microRNAs in the neurite. Others have found that one microRNA is required for controlling neurite growth in response to cAMP.

We propose to screen the full complement of microRNAs for those affected by cAMP and to determine whether they can enhance neurite growth in Dr. Filbin's sensitive culture system. These microRNAs, by reversing the inhibition of neurite growth caused by proteins from injured spinal cord, are likely to promote regeneration. Identifying microRNAs that enhance neurite growth will lead to the use of these microRNAs as therapies in spinal cord injury.

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PRINCIPAL INVESTIGATOR – Renping Zhou, Ph.D.

Rutgers, The State University of NJ
Department of Chemical Biology
Basic Science Proposal
Grant Award - $400,000

Proposal Title: Regulation of Spinal Sensory Afferent Ingrowth by B-ephrins

It is anticipated that the experiments outlined in this application will elucidate novel molecular mechanisms that regulate directed neuronal growth within the developing vertebrate spinal cord. These mechanisms may provide novel targets for the development of drug therapies to facilitate spinal cord regeneration.

In particular, we hope to identify specific cell surface molecules that control the precise time at which nerve fibers from the peripheral nervous system enter and grow within the developing vertebrate spinal cord. Importantly, these peripheral projections form highly specific connections with neurons in the spinal cord and, ultimately, the brain. Therefore, the molecules that control the timing and direction of their growth necessarily play critical roles in establishing the functional circuitry of the spinal cord and, in turn, facilitate proper communication between the brain and the rest of the body. Furthermore, since these projections mediate multiple sensory modalities the molecular mechanisms that should be uncovered by this work are likely to ensure the proper perception of pain and temperature, and facilitate the control of muscle reflexes.

The proposed experimental plan involves visualizing the distribution of particular cell surface proteins in the spinal cord, assessing the ability of these proteins to inhibit the growth of cultured axons, and determining whether blocking the function of these proteins leads to defects in spinal cord development. These approaches should identify molecules that regulate proper axon guidance in the embryonic mammal spinal cord through inhibitory/repulsive mechanisms. Since these types of molecules are thought to limit the regenerative capacity of the adult spinal cord, the proposed studies may ultimately lead to the design of therapies that promote recovery from spinal cord injury by stimulating the regeneration of damaged nerves.

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PRINCIPAL INVESTIGATOR – Ron Weiss, Ph.D.

Princeton University
Department of Electrical Engineering
Basic Science Proposal
Grant Award - $199,562

Proposal Title: Artificial Signaling Pathways for Tissue Regeneration

Spinal cord injury by trauma or disease is severely debilitating, typically causing significant paralysis in the victim. The major therapies currently in use are primarily aimed at preventing continued tissue damage via the inflammatory response and oxidative destruction or by increasing functionality of affected limbs and muscles via intense physical therapy. While these therapies manage to rescue some function, scientists have been hard pressed to find more effective treatments. Transplantation of undamaged adult spinal cord cells may eventually be an effective avenue for therapeutic intervention, however this therapy is limited in its ability to fully regenerate the precise patterning of cell types found in the spinal cord and is plagued by complications due to tissue rejection and lack of appropriate environmental cues. Stem cells are another potential source of transplantable material with recent studies in injured mice demonstrating that these cells show promise in recovering at least partial functionality in spinal cord injury. A major barrier to realizing stem cell potential is the inability to reliably direct these cells toward specific cell fates. For spinal cord repair it is important to ensure that appropriate cell lineages normally found in this tissue are produced in sufficient numbers, with the proper 3D structure, and that once the structure is rebuilt, the cells know when to stop production of mature tissue.

Although the mechanisms by which mature cells are produced from stem cells are poorly understood, a number of chemicals that function as genetic cell fate regulators in stem cells have been identified. Cell fate regulators direct stem cells to become specific cell types in mature tissue. We propose using genetic engineering to create artificially controlled signaling pathways inside mouse embryonic stem cells. We will potentially be able to use these pathways to trigger defined production of different cell fate regulators relevant to spinal cord development. This system will be self sustaining and will only need a transient manually applied signal to activate cell-cell communication and the subsequent expression of an appropriate cell fate regulator.

Specifically, we propose to produce in vitro a 3D pattern of different tissue types depending on cell-cell signaling and resultant choice of cell fate regulator. Eventually we would like to be able to program these engineered cells to produce correctly organized 3D spinal cord tissue. The joint expertise of the Weiss and Lemischka labs will facilitate the rapid progress of studies in this proposal. The Weiss lab has pioneered the design and implementation of artificially controlled genetic circuits. Lemischka is a leader in stem cell research for a number of years. We anticipate that the successful completion of the studies in this proposal will lay solid groundwork for broad applications in stem cell mediated repair of damaged tissues, especially the spinal cord.

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PRINCIPAL INVESTIGATOR – Mengquing Ziang, Ph.D.

UMDNJ – Robert Wood Johnson Medical School
Center for Advanced Biotechnology & Medicine
Basic Science Proposal
Grant Award - $400,000

Proposal Title: Role of Brn3 Genes in Spinal Neuron Development and Survival

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 cell types, 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.

Since 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 differentiation and survival of sensory and motor neurons during spinal cord development. It will focus on the roles of the Brn3 POU domain transcription factors in the development of dorsal interneurons. Brn3 factors display several salient features as crucial regulators of sensory interneuron development, leading to the speculation that they may play key roles in controlling the differentiation and/or survival of distinct dorsal interneuron types of the spinal cord. 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 sensory neurons in the chick system. We will analyze developmental defects in spinal cords of Brn3 single and double mutant mice and investigate the roles of Brn3 factors in the specification of interneurons by misexpression in spinal cord progenitor cells. Together, these proposed studies are expected to identify the developmental and genetic processes that Brn3 factors regulate and hence may yield important novel insights into the molecular mechanisms governing spinal neuron development and maintenance.

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FELLOWSHIP GRANT RECIPIENTS:

PRINCIPAL INVESTIGATOR – Kevin Christian Donahue

UMDNJ – New Jersey Medical School
Department of Neurology & Neuroscience
Graduate Fellowship Grant Award - $60,000

Proposal Title: Toll-Like Receptor 9 Mediated Neuropathology in the Spinal Cord

Spinal cord injuries (SCI) affect approximately 250,000 people in the United States at present, and have serious consequences for the lives of patients. Therefore, it is imperative that we continue to uncover the biological mechanisms that cause damage after the initial injury so we can develop effective treatments to combat this process. SCI leads to extensive damage to nerve cells. Some of these nerve cells die as the consequence of the initial trauma whereas others are injured subsequently, due to deleterious changes that occur hours or days after the first mechanical impact. It is believed that one type of cell that resides in the central nervous system (CNS) called microglia are among the first responders to traumatic injury of the spinal cord by modifying their appearance, increasing their number, and altering the substances they secrete. These changes collectively describe a process known as cellular activation. Some of the substances that are secreted by activated microglia have harmful effects on nerve cells. The materials that are released by microglia in response to specific activators and the subsequent mechanisms that injure nerve cells after SCI are poorly defined. Delineation of such mechanisms and characterization of microglia-to-neuron signals in response to specific stimuli are of critical importance, as this may lead to the identification of novel targets for therapeutic interventions which prevent the aggravation of clinical symptoms. Recently, it has been suggested that during SCI, DNA is released from damaged cells and has the capacity to interact with microglia via proteins located on or inside the cell called toll-like receptors (TLRs). There are several different TLRs and the present study will focus on one of them, TLR9. We will especially study TLR9 because it has been reported that binding of DNA or DNA-like agents to TLR9 causes microglia to produce substances that ultimately induce neuronal death when the two cells are grown together in experimental conditions. Yet, little is known about the substances secreted by microglia following stimulation of TLR9 and the molecular changes that occur within nerve cells when exposed to the materials released by microglia.

Therefore, we propose 1) to characterize the substances that are produced by microglia in response to stimulation of TLR9 in order to determine which of these substances are injurious to neurons; 2) to identify the neuronal mechanisms which get affected when nerve cells are exposed to materials released by microglia following stimulation of TLR9. We will especially focus on mechanisms that regulate the concentrations of calcium within the neuron. We have previously shown that these mechanisms are of critical importance for the integrity of spinal cord neurons; and 3) to assess whether therapeutic blockage of TLR9 in an animal model of SCI prevents deterioration of clinical symptoms.

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PRINCIPAL INVESTIGATOR – Berangere Pinan Lucarre

Rutgers, The State University of NJ
Department of Molecular Biology & Biochemistry
Postdoctoral Fellowship Grant Award - $100,000

Proposal Title: Genetic Dissection of Neuronal Regeneration in C. elegans

Spinal cord injury is a devastating event for victims and families. Tragically, we lack effective interventions that limit immediate damage and promote regeneration. A more detailed understanding of the molecular mechanisms of neuronal regeneration will be required for design of novel and effective therapies that could shift treatment goals from palliative care to restoration of function. We study molecular influences on 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 directly sever, and observe the regeneration of, axons within the living animal as well as the ability to conduct exhaustive genetic hunts for mutations that impact a process of interest (such as those that modulate neuronal regeneration). In general, experiments that are implausible 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 decipher the molecular basic rules of a given process in the C. elegans and then use this information to address the function of homologous 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 influence this process in humans--manipulation of the protein products of these genes is a highly plausible strategy to ameliorate the devastating consequences of spinal cord injury. Focused laser pulses can sever individual neurons in living C. elegans. Remarkably, axotomized neurons can functionally reconnect. To our surprise, we found that an apoptosis cell death caspase protease called CED-3 (which is normally needed to promote developmental cell death) is needed for efficient neuronal regeneration! This observation holds high clinical relevance in that blocking caspase activity consequent to injury is a proposed treatment for limiting nerve damage following injury. Our results suggest that such treatments might actually limit capacity for regeneration, and urges rethinking of anti-caspase strategies.

Here I propose to determine the mechanism by which CED-3 impact regeneration and to identify additional regeneration genes with three key aims: 1) I will determine whether the other components of the apoptotic pathway are required for regeneration, 2) I will determine when, where, and with what activity CED-3 protease contributes to regeneration, and 3) I will conduct a genetic screen for novel mutations that suppress regeneration in vivo. The anticipated outcome of my project will be a markedly extended mechanistic understanding of how CED-3 protease contributes to regeneration across species and new gene discovery that will inform on physiological relevant mechanisms and inspire novel therapeutic strategies.

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PRINCIPAL INVESTIGATOR – Shaunak Kamat

Rutgers, The State University of NJ
Department of Molecular Biology & Biochemistry
Graduate Fellowship Grant Award - $60,000

Proposal Title: Molecular Mechanisms of Action of an Anti-Necrosis Drug

In spinal cord injury some neurons are directly damaged, but many others die during a phase of secondary necrosis induced by exacerbated ion channel activity. Blocking or delaying secondary neuronal necrosis would significantly limit debilitating consequences of injury, and is a critical goal in spinal cord injury research. A recent publication described an impressive anti-necrosis effect of a compound called necrostatin on injured neurons as well as on neuronal death in a rat ischemia model. Although necrostatin is a fairly specific inhibitor of necrosis (as compared to apoptosis), virtually nothing is known of its mechanism of action. The step at which necrostatin acts and its molecular target(s) have not been identified.

In the Driscoll laboratory, we study molecular mechanisms for injury-induced necrosis and regeneration in a simple animal amenable to genetic and molecular manipulation--the nematode Caenorhabditis elegans. A key advantage of this system is that the nervous system is visible in the living organism and genes modulating apoptotic, necrotic, and autophagic cell death have been identified. Since most basic biological processes, including the cell death, occur by molecular mechanisms conserved from nematodes to humans, we believe we can identify critical molecules and 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.

Importantly, we have preliminary data that indicates necrostatin is effective against necrosis in C. elegans, suggesting the mechanism of necrostatin action is conserved across species. Therefore, we plan to exploit the experimental features of C. elegans to identify how necrostatin acts to block neuronal death and to identify its molecular targets. Our Aims are - Aim 1: To optimize conditions for necrostatin inhibition of necrosis in C. elegans, Aim 2: To test necrostatin effects on necrotic, apoptotic and autophagic death paradigms in this model, Aim 3: To determine where in the necrotic pathway necostatin acts, testing available genetic steps of the necrosis pathway, Aim 4: To identify mutations that block necrostatin action to identify physiological targets, and Aim 5: To determine if necrostatin impacts proficiency for neuronal regeneration.

Overall, this project will markedly advance understanding of the physiological action of necrostatin in necrosis and suggest a model for how necrostatin exerts it neuroprotective effect in mammals. Moreover, data will highlight pathway steps for therapeutic intervention and will extend basic understanding of necrosis mechanisms. This data may provide critical insights that can be exploited in spinal cord injury.

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PRINCIPAL INVESTIGATOR – Andrew Voyiadjis

Rutgers, The State University of NJ
Department of Biomedical Engineering
Graduate Fellowship Grant Award - $60,000

Proposal Title: In Vitro/In Silico Comparison of Neurite Arborization

On average, one serious spinal cord injury occurs every day in New Jersey*. There is no sensible way to calculate the human cost of these injuries. The lifetime financial cost for caring for these citizens – most of whom are younger than 40 – ranges from half a million dollars to over 2 million dollars depending on severity**. At an average cost of a million dollars in new obligations every day, this is clearly a problem worthy of significant public attention. Numerous laboratories worldwide are consequently actively engaged in pharmacological, neuroprotective, surgical and stem cell therapies intended to promote regrowth of neurons following Spinal Cord Injury (SCI).

In this proposal, we observe that although existing efforts to regenerate spinal neurons are crucial to the restoration of function following SCI, they are not by themselves sufficient. In order to achieve the goal of functional recovery, regrowing neurons must in addition find a way to reach specific and appropriate target locations - if neurons do not reach the right targets, they simply will not restore function.

In this proposal we show that because of the complexity of spinal connections, the a priori chance of a nerve axon reaching a specified target in the spinal column without inducing neurite branching can be expected to be less than 1 in a million. We believe, however, that an integrated program of computational simulations combined with biological experiments can identify therapeutic strategies that will successfully increase the likelihood that a regrowing neurons will reach usable targets and thereby restore function. In future therapies, these branching strategies would consist of injecting specified chemical agents into particular locations in the spinal cord increasing the axon search area to effectively ensure that regrowing neurons make functional connections. With these signals, neurons can behave like a search and rescue team, spreading out to explore more paths and by doing so improve the chances of finding a hidden target.

We propose to attack this problem by combining well established techniques including computational modeling of neurite outgrowth, culturing cells on surface modified micropatterned substrates, and statistically significant experimental designs that ensure robust and reliable comparisons between in silico and in vitro quantitative analyses. This work will produce an experimentally validated, predictive model for neuronal growth that will inform future therapeutic interventions by providing specific and concrete data on where injections of axonal branching factors (BFs) must be introduced to ensure that regrowing neurons make connections that successfully restore sensory and motor function following SCI.

*Center for Disease Control Spinal Cord Injury Fact Sheet: http://www.cdc.gov/ncipc/factsheets/scifacts.htm
**Spinal Cord Injury Facts, Spinal Cord Injury Statistics Updated August, 2004

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PRINCIPAL INVESTIGATOR – Gauri V. Kulkarni

UMDNJ – Robert Wood Johnson Medical School
Department of Pathology
Postdoctoral Fellowship Grant Award - $100,000

Proposal Title: A C-type Lectin-like Receptor in Axon Growth and Guidance

Spinal cord injuries and related neuronal disorders are one of the leading public health concerns with an unmet medical need. Thousands of New Jersey residents suffer from spinal cord and related injuries, which affect their health and socio-economic life to a great extent. These injuries cause damage to the motor axons (which control movement) and sensory axons, that results in breaking the connections between neurons and target cells and thus, resulting in paralysis. Unfortunately, the ability to grow new axons is limited, resulting in incomplete recovery. Therefore, future treatments are required to target the regeneration of damaged axons following injury and help to restore the lost sensory or motor functions. Current research advancements towards understanding the basic mechanism of axon growth and guidance have a strong potential to create breakthrough therapies to treat people with disability caused by spinal cord injuries.

The proposed study will take help of powerful genetics and cell biology approach using a simple, nematode model system, C. elegans. Several key molecules that are involved in axon guidance during the development of human nervous system were first discovered in C. elegans. Most of these guidance molecules persist in developed adult nervous system. Current studies show that expression of some of the axon guidance molecules are dramatically changed after the spinal cord injury, which could be one of the major causes of limited axonal growth after the injury.

The goal of this proposal is to understand the molecular mechanism, which regulates development and regeneration of motor and sensory axons. This will be accomplished by studying the function of a protein, CLEC-38. This is a newly identified protein that is involved in axon growth and the axon's ability to make appropriate connections. The proposed research will seek to determine how the CLEC-38 protein is able to improve the ability of axons to grow and form appropriate connections. A better understanding of the molecular mechanism of axon guidance and circuit formation is likely to be beneficial towards development of new therapies to help repair of damaged spinal cord.

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PRINCIPAL INVESTIGATOR – Tara P. Cominski

UMDNJ – Robert Wood Johnson Medical School
Department of Neuroscience & Cell Biology
Graduate Fellowship Grant Award - $60,000

Proposal Title: Opioids and Cell Proliferation Following Spinal Cord Injury

Endogenous populations of neural stem cells exist in the spinal cord, which serve as potential targets for spinal cord injury (SCI) treatment. However, understanding the characteristics of these proliferative populations and the factors that regulate them is necessary before they can be manipulated and used for treatment following SCI.

The focus of this research project is to quantify and characterize the endogenous stem cell population that exists in the adult spinal cord under normal circumstances and following SCI.

In aim 1, we will examine the stem cell population in the spinal cord when opioid receptor function is disrupted. The endogenous opioid system is the focus of our proposal because it has been shown to effect proliferation of central nervous system cells and to be involved in neuroprotection following SCI.

The second aim of this proposal will focus on the endogenous stem cell population in the spinal cord following SCI. We will determine if there is a differential response following injury in both cell proliferation and in locomotor recovery when opioid receptor function is disrupted. Following SCI there is a stage of glial cell proliferation leading to the formation of a glial scar, which is detrimental to repair and regeneration of the spinal cord. This process may be exaggerated when the opioid system is disrupted and thus may lead to a reduction in locomotor recovery following SCI. Since this stage of cell proliferation is a potential target for therapeutic intervention, future applications of this research are to develop treatments that increase or decrease proliferation in order to promote locomotor recovery following SCI.

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PRINCIPAL INVESTIGATOR – Geoffrey Hunt

Princeton University
Department of Molecular Biology
Graduate Fellowship Grant Award - $60,000

Proposal Title: Extracellular Matrix-Induced Differentiation of Stem Cells

The primary damage of a spinal cord injury affects cells that cannot regenerate. A promising technique for relieving this damage involves transplanting cells into the spinal cord, in order to either regenerate the damaged cells, or stimulate the endogenous cells to reactivate. The most successful techniques so far use embryonic stem (ES) cells, which have the ability to form any tissue in the body. These cells are changed, through a process known as differentiation, outside of the body into cells that are primed to function in the spinal cord. Once inside the body, these cells, called neural precursors, have been shown to be able to begin to restore function to the spinal cord. Unfortunately, the differentiation process that is used to prime the cells is inefficient, and the subsequent therapy and recovery is less than perfect. Thus, a basic knowledge of the mechanisms responsible for differentiation of ES cells is required to optimize cell-based therapies.

The Extracellular Matrix (ECM) is a network of proteins that is the primary structural component in all tissues. ECM proteins are known to affect a variety of cellular processes, including differentiation, and are used in several protocols involved in generating neural precursors. It is therefore critical to understand the effects of these proteins on ES cell differentiation. I am specifically studying the ECM protein fibronectin. While fibronectin is known to influence differentiation in a general way, the specific effects of fibronectin on differentiation of ES cells are not well known.

For my studies, I am using ES cells that are fluorescent green. These cells lose this green signal when they differentiate, thus providing a simple way to test for differentiation. My preliminary work has shown that ES cells growing on fibronectin are spread out, and have a very week green signal, indicating that the cells have differentiated. My hypothesis is that fibronectin causes cells to spread, thus increasing their total area, which causes them to differentiate. I will grow ES cells on fibronectin, and change individual parameters (such as concentration and conformation) to see how these changes affect differentiation. I will analyze the kinetics of differentiation by quantifying the amount of fluorescent green signal coming from cells. To test if cell area is related to differentiation, I will make a quantitative correlation between cell area and the amount of green fluorescence from individual ES cells grown on fibronectin. I will also analyze the type of differentiation by looking for decreased expression of markers present in undifferentiated cells, along with increased expression of markers of neural markers as cells differentiate.

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PRINCIPAL INVESTIGATOR – EunChan Park

Rutgers, The State University of NJ
Waksman Institute/Department of Genetics
Graduate Fellowship Grant Award - $60,000

Project Title: The Role of p38 MAPK in GluR Trafficking and Excitotoxicity

Spinal cord injury (SCI) is a distressing illness that results in the loss of sensory and motor function. Affected individuals experience the loss of mobility, sensation, and autonomic function, and experience chronic neuropathic pain. Neuron damage by SCI results from mechanical damage (e.g., traumatic injury) or ischemia (oxygen deprivation) caused by breakdown or obstructions 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, damaged neurons release large quantities of the neurotransmitter glutamate into surrounding tissue. Glutamate overactivate receptors present on surrounding neurons, resulting in calcium influx and oxidative stress, which kills the neurons (this is termed excitotoxicity). These dying neurons release more glutamate, leading to waves of dying neurons spreading out from the injury site. We aim to study excitotoxicity using a genetic approach in C. elegans, which uses glutamate receptors in sensory circuits that are similar to circuits in the human nervous system. The Rongo lab studies genes that regulate these receptors. 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 mutations in genes that regulate glutamate signaling or intracellular calcium levels can block neurodegeneration. This affords us an easy and inexpensive method (forward genetic screening) for identifying other genes involved in this cell death process, and funding of this proposal would allow the Rongo lab to expand our studies into the field of glutamate-mediated excitotoxicity and SCI. We have identified 2 new factors that regulate glutamate receptor function: p38 MAPK and RPM-1. As p38 is involved in oxidative stress, our findings provide a new link between glutamate and oxidative stress. We propose to determine the mechanism by which p38 MAPK and RPM-1 function and modulate excitotoxic death.

This proposal satisfies the goals of the NJCSCR in two ways. First, we will determine the mechanism of excitotoxicity, and identify agents that block glutamate receptor activation and limit damage. By identifying and characterizing these agents, we should identify key targets for new therapeutic interventions that limit neuronal damage following SCI. 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 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 have human equivalent genes playing a similar role in humans, suggesting our findings are likely to be applicable to human health.

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PRINCIPAL INVESTIGATOR – Ryan A. Norman

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Graduate Fellowship Grant Award - $60,000

Proposal Title: The Role of Tulp3 in Axon Guidance and Neuronal Development

Restoration of neural function in individuals with spinal cord injury (SCI) will rely on regenerating the damaged cells and ensuring their proper connectivity. By understanding how the cells are normally generated and connected during embryonic development, we can design therapies to recapitulate this in the treatment of SCI.

Neurons of the mammalian spinal cord develop from two populations of cells that grow, migrate, and differentiate through a strictly timed process of organization into structures called the neural tube and the neural crest, which surrounds the neural tube. Cells within the neural tube create the central nervous system by developing sensory neurons to transmit information from the environment, motor neurons to coordinate muscle function, and interneurons to network these neuron populations in the spinal cord and brain. Sensory input from the limbs and organs is sent to the central nervous system through neuronal derivatives of the neural crest cells, called the dorsal root ganglia. These physically link the peripheral systems to the spinal cord through cellular extensions called axons.

Our research focuses upon characterizing components and mechanisms that coordinate the initial stages of neuron patterning and migration within the embryonic mouse spinal cord. Previous groups' work has shown that location within the neural tube is key as cells within the dorsal half of the neural tube will produce central nervous system sensory neurons while motor neurons develop in the ventral neural tube. Further research identified that the protein signal responsible for motor neuron development, Sonic Hedgehog, is released from a structure called the notochord close to the ventral neural tube whereas dorsal areas receive little or no Hedgehog. Exactly how Sonic Hedgehog molecularly generates the ventral neurons is poorly understood. Also unclear is how at later stages in development the dorsal root ganglia neurons perceive their molecular environment and send their axons properly to the spinal cord. I am working to clarify both of these processes by characterizing Tulp3, a gene that when mutated in embryonic mice triggers excessive motor neurons to differentiate and causes premature and misguided dorsal root ganglia axon migration. Unusually, the patterning and additional axon guidance defects mirror a mutation we study in a novel Hedgehog pathway component, Rab23, whereas most mutations in Hedgehog components affect neuronal patterning only. This may indicate that some pathway proteins may have distinct roles in both patterning and axon guidance. To understand how Tulp3 regulates Hedgehog-dependent neuronal patterning and dorsal root axon guidance, I will determine with what proteins Tulp3 interacts, determine Tulp3 location within developing neurons, and manipulate Tulp3 location with drug-treatment to monitor changes in patterning and axon migration.

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PRINCIPAL INVESTIGATOR – Maria Nuri Royo-Gascon

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Graduate Fellowship Grant Award - $60,000

Proposal Title: Guiding Axonal Regeneration with Piezoelectric Polymers

Total or partial interruption of nerve pathways, leads to different degrees of physical impairment. If nerve regeneration could be enhanced and controlled, a high level of functioning would be restored; however, this regeneration does not occur spontaneously. The chance of discovering a method to reconnect the neural pathway increase by addressing the same issue from several different perspectives. Therefore, current approaches to re-grow axons on the spinal cord are based on: a) cell implantation, b) chemical agents, c) interactive substrate materials, d) mechanical stimuli and e) electrical stimuli. Several such techniques are combined in the current project presented here: the application of electrical fields to the injured spinal cord by means of a piezoelectric polymer substrate (PZLA) to promote directional growth of the neurons. While the response of nerve cells to mechanical and chemical stimuli is well understood, there is a lack of knowledge concerning the mechanism or mechanisms by which these cells respond to electric fields. Nevertheless, it is known that they are sensitive to electrical signals, since communication in the nervous system itself is based on electrical action potentials.

Preliminary studies have shown that cells grow and align on the surface of PZLA under electrical fields produced by the vibration of PZLA polymer films. There are other precedents for using oscillating electrical fields to enhance nerve cell growth. Thus, electrical stimulation has the ability to act as an important factor in the enhancement of nerve cell growth and should be studied within the context of spinal cord injury. In this project, electrical fields will be generated by using a piezoelectric polymer, (PZLA), instead of the traditional electrodes usually implanted to generate such fields. Piezoelectricity is a rare property by which the mechanical deformation of a material causes an electrical field. This couples the effects of both a biodegradable substrate and electric fields, in a single material with the same purpose in mind: growth enhancement. In addition, PZLA meets two necessary conditions for a body implant. It is biocompatible, which ensures no rejection problems, and completely biodegradable, with a degradation rate that can be controlled by the crystallinity and thickness of the material. This ensures degradation by the body at a scheduled time, when the wound is healed. Directional growth is another characteristic of this approach. Not only nerve cell growth but also directional growth is important to reconnect the neural pathway. In preliminary experiments, electric fields from PZLA have been shown to align cells, indicating that such guidance is possible.

The final aim of this project is developing a graft made of PZLA substrate to fill the gap between neurons. The draft will create an appropriate electrical field in axons to promote growth in the desired direction and achieve reconnection in spinal cord injuries.

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