
# DIRECTORY OF GRANT AWARDS
# 2010 B GRANT CYCLE

# NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

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

**DECEMBER 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 2010 B 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.

## 2010 MEMBERSHIP INFORMATION

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# NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

# GRANT AWARDS

## INDIVIDUAL RESEARCH GRANT RECIPIENTS:

**Jonathan Eggenschwiler, Ph.D. – Principal Investigator**
Princeton University – Molecular Biology
Grant Award: $400,000

Project Title: *The Role of Trpm6 in Shh Signaling and Neural Cell Identity*

Roughly 250,000 Americans suffer from spinal cord injuries (SCI). Such injuries have devastating consequences for the quality of life for SCI patients and their families in addition to causing a substantial economic burden. Basic and clinical research is paving the way for the development of new therapeutic approaches to treating SCI patients with the hope of restoring significant motor and sensory function. One promising avenue being aggressively pursued is regenerative and transplantation therapy based on the use of embryonic and neural stem cells. One important aspect of this approach is to identify methods of efficiently producing large numbers of individual neuronal subtypes in culture for transplantation in SCI patients.

The Sonic Hedgehog (Shh) signaling pathway controls specification, proliferation, and survival of a large variety of neural cell fates in the developing spinal cord including motorneurons and many classes of interneurons. Thus, harnessing this pathway for the generation of distinct types of neurons from multipotent progenitor cells has proven to be extremely useful. However, controlling this pathway in mammalian neural progenitors with quantitative, spatial and temporal precision will rely on a better understanding of the intrinsic and extrinsic factors that mediate Shh signal transduction. Functional analysis of mouse genes controlling Shh signaling has been very successful in this respect.
Here, we propose to study a new and exciting dimension of mammalian Shh signaling that centers on a channel-kinase protein called Trpm6, which has been previously shown to control magnesium homeostasis. We will investigate how the Shh signaling pathway and neural cell fate choice are regulated by Trpm6 using animal and cell culture models. In addition, we will investigate whether this function of Trpm6, and the related channel-kinase with which it forms a protein complex, Trpm7, controls the Shh pathway through its role in magnesium homeostasis or by modifying proteins that act directly within the Shh pathway. The long term goals of this project are to identify ways to modulate Trpm6 function (and, possibly, intracellular ion concentrations) as a means of controlling the Shh pathway in the generation of new neurons for the repair of damaged tissues in the injured spinal cord.

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**Michael Matise, Ph.D. – Principal Investigator**
University of Medicine & Dentistry New Jersey – Robert Wood Johnson Medical School
Grant Award: $400,000

Project Title: *Signaling Pathways Regulating Axon Remyelination*

Injuries or CNS diseases affecting the spinal cord typically result in the local loss of myelin-producing Oligodendrocytes (OLs). These cells serve a critical and unique function in the CNS, providing a lipid sheath that enwraps nerve processes to facilitate signal conduction. In the absence of myelination, neural transmission is severely compromised. The success of efforts to restore function following spinal cord injury or disease depends on the proper reconstitution of damaged circuits, to which OLs make a crucial contribution. Therefore, a better understanding of the re-myelination process will improve our ability to develop successful therapeutic strategies to treat this and other function-compromising disorders.

Numerous studies have demonstrated that the adult mammalian CNS contains un-differentiated adult OL progenitors (OPCs) located in the white matter and parenchyma that can give rise to new re-myelinating OLs following injury or focal de-myelinating lesions, such as those that occur in Multiple Sclerosis. Interestingly, comparative studies have shown that the re-myelination process replays to a large degree the normal developmental program for these cells, suggesting that our understanding of this process in adults can be guided by insights gained from developmental studies.

In this proposal, we will address these issues by examining the signaling mechanisms that direct the formation of OLs following de-myelinating lesions of the adult spinal cord. Based on preliminary data from our lab and work published elsewhere, we propose that two signaling pathways that play a critical role during CNS development and embryonic OL production will also function in adult OPCs to direct re-myelination following injury. Specifically, we will assay whether the Sonic Hedgehog (Shh) and Wnt pathways function in adult OPC cells to regulate their response to such injuries. For this, we will use a rodent injury model that selectively damages OLs in the spinal cord in combination with a new transgenic mouse line that will allow us to focus specifically on their response to injury.

If we find that either or both of these pathways are involved in promoting re-myelination following injury, it will be possible to design therapeutic strategies that could be used to treat patients suffering from such disorders to improve recovery of neural signaling function.

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## EXPLORATORY RESEARCH GRANT RECIPIENT:

**Prabhas Moghe, Ph.D. – Principal Investigator**
Rutgers, The State University of New Jersey – Biomedical Engineering
Grant Award: $200,000

Project Title: *Nanobioactive Scaffolds for Management of Spinal Cord Injury*

This program proposes to use technological advances in nanobiotechnology and biomaterials for the goals of creating microconstructs for transplanting neural stem cells to sites of spinal cord injury. The nanobiotechnology component relates to the design and fabrication of biocompatible albumin nanoparticles that are modified to present biologically active signals based on L1 adhesion molecule. These signals are hypothesized to promote adhesion and differentiation of neural stem cells to neuronal cells, which are the cells whose activities promote repair and functional recovery of spinal cord injuries. The biological peptide/functionalized nanoparticles will be incorporated within polymeric fibrous scaffolds electropsun from synthetic polymers that are biodegradable and tailored to promote cellular ingrowth and expansion. The combination of biological nanoparticles and 3-D constructs is hypothesized to promote the biological activity of human neural stem cells (pre-differentiated from human embryonic stem cells) to be grown and transplanted on the scaffolds. This project will examine the effect of controlling the geometry of the scaffolds and incorporation of the bioactive nanoparticles on the degree of neural stem cell differentiation in vitro and possible functional recovery of spinal cord injury using mouse spinal cord lesion models in vivo.

If successful, this project can yield novel methods to design bioactive, implantable materials for cell transplantation therapies. These methods in conjunction with advances in stem cell sourcing can significantly impact the efficacy and outcomes of spinal cord injury management.

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# FELLOWSHIP GRANT RECIPIENTS:

**Jeffrey Barminko – Principal Investigator**
Rutgers, The State University of New Jersey – Biomedical Engineering
Grant Award: $60,000

Project Title: *Encapsulated Mesenchymal Stem Cells for Spinal Cord Injury*

According to the Annual Report (2006) of the Spinal Cord Injury Information Network, there are ~ 11,000 new cases of SCI annually, and more than 253,000 people are living with devastating disabilities resulting from SCI. At this time, the average age of a patient at the time of injury is 38.0 years. Thus, SCI affects individuals in the prime of their lives, causing serious harmful effects on their quality of life with a considerable financial impact on the healthcare system. Victims of SCI experience a tremendous change in life style requiring much healthcare system support. Reduced SCI recovery is caused largely by tremendous immune response based inflammatory responses, resulting in faulty neuron regeneration in the hostile secondary injury environment. It has been shown, in several animal models that mesenchymal stem cells (MSCs) can modulate the immune response and promote tissue repair. In addition, several reports have demonstrated that MSCs can promote neuronal regeneration in animal spinal cord injury models. However, in these studies neither the long term survival nor the localization can be adequately controlled, limiting the potential effectiveness of MSC implantation therapy for SCI treatment. In order to overcome these obstacles and to investigate the role of local MSC infusion in SCI treatment, we propose to develop an alginate microencapsulation system. We hypothesize that encapsulation will prolong MSC survival thereby resulting in a localized anti-inflammatory response, and thereby assist in generating an environment conducive to neuronal regeneration. At the completion of these studies, we expect to: i) develop an effective MSC encapsulation method, ii) using a rat SCI model, test the viability and function of the encapsulated MSCs.

The objective of the proposed study is to investigate MSCs as a potential treatment of traumatic spinal cord injury. The central hypothesis to be tested here is that introduction of encapsulated MSCs around the lesion will lead to a marked reduction in inflammation. The rationale is that MSC transplantation near the site of injury can simultaneously produce a localized anti-inflammatory effect, prevent cell death, and enhance neuronal regeneration counteracting the effects of secondary injury. These studies will therefore pave the way to testing MSC based SCI cell therapies in large animal models and ultimately humans and assist in identifying interventional protocols to ameliorate the devastating effects of secondary SCI injury.

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**Gary Monteiro – Principal Investigator**
Rutgers, The State University of New Jersey - Biomedical Engineering
Grant Award: $100,000

Project Title: *Bimodal Delivery of L1 for Spinal Cord Regeneration*

The spinal cord has a limited ability to regenerate. The wound that forms, glial scar, during SCI hinders the functional recovery of patients. In addition, the loss of cells that have limited ability to divide further reduces the odds of recovery. To date there is no cure for SCI. However, with the advancements in tissue engineering and the advent of stem cells, a glimmer of hope exists. Stem cells have the potential to differentiate into all cells within the body including those injured during SCI. Tissue engineering provides a means to deliver these cells to the injury site within materials that may promote the regeneration of damaged cells as well as guide the differentiation of implanted cells towards those cell types that have been depleted. Taken together, these approaches address two of the many challenges that limit the recovery of those inflicted with SCI.

Herein, we propose to develop a cellular-material therapeutic that can be injected into the site of injury and modifies the microenvironment surrounding the wound to allow for the generation of axons and promotes the differentiation of resident as well as injected stem cells towards cell types that have been lost during injury. In addition, this cellular-material therapeutic will minimize the infiltration of inflammatory cues and cells that cause the formation of the glial scar in the first place. Our efforts will focus on the cell adhesion molecule L1. The L1 adhesion molecule plays an important role in axon guidance and cell migration in the nervous system. It has also been identified to play a role in the guiding stem cells differentiation towards a neuronal lineage. We will introduce immobilized L1 adhesion cues on self-assembling collagen fibers to guide the differentiation of included L1 over expressing stem cells toward a neuronal lineage and minimize the infiltration of reactive astrocytes and macrophages into the injury site.

We sincerely believe that the repair of injured spinal cords is a reachable goal and will take the efforts of several talented individuals and organizations working together to attain it. Any therapeutic that ultimately cures SCI will be combination of several factors, including cellular therapeutics, engineered materials, chemical cues, surgery and rehabilitation. Optimizing each of these facets individually and in combination will be critical for full functional recovery.

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**Aruni Singamkutti Arachchige Don, Ph.D. – Principal Investigator**
University of Medicine & Dentistry New Jersey-Robert Wood Johnson Medical School
Grant Award: $150,000

Project Title: *Molecular Mechanisms of mTOR-mediated Axonal Outgrowth*

As many as 12,000 individuals nationwide, including approximately 300 New Jersey residents, are paralyzed each year from a spinal cord injury (SCI). These injuries have devastating long-term effects on the individuals, their families, and on the health care system. Because currently available therapies are not very successful, SCI patients are in dire need of new and more effective therapies. SCI resulting from either a trauma or disease damages nerve fibers that control autonomic, motor, and sensory functions. One of the main strategies in SCI therapy is to promote re-growth of damaged nerve fibers or "axons". Investigating the normal mechanisms of axonal outgrowth is important for identification of potentially new drug targets for SCI.

Our main research focus is on the mammalian target of rapamycin (mTOR), a central protein involved in the control of cell growth and metabolism. mTOR is in fact an important therapeutic target for a number of major human diseases. Recent research shows that mTOR regulates several central nervous system (CNS) functions, including neuronal growth and survival. Although a role for mTOR in CNS functions has clearly been demonstrated, how mTOR controls these functions are less understood. Importantly, a new study demonstrated that mTOR activity promotes re-growth of damaged axons following CNS injury. Furthermore, we isolated spinal cord sensory neurons from rats and show that promoting mTOR activity enhances nerve fiber growth and inhibiting mTOR blocks this growth. These findings suggest that mTOR does indeed play an important role in the growth of spinal cord neuronal processes.

Here, we will investigate the molecular mechanism by which mTOR controls axon growth. Our preliminary findings suggest a potentially novel mechanism by which mTOR regulates growth of axons. We discovered a new protein which we refer to as the Golgi Receptor Protein (GRP). Our studies reveal that GRP belongs to a family of proteins highly expressed in the nervous system that are important regulators of axon growth. In neuronal cells, several members of this protein family are located at a particular site called the Golgi apparatus. The Golgi apparatus is a compartment implicated in functions such as axon outgrowth. It is well-known that segregation of signaling proteins to specific sub-cellular sites is a common mechanism utilized by cells to control diverse biological processes. Therefore, we will test whether GRP anchors mTOR to the Golgi apparatus to activate its signaling and regulate axonal outgrowth. We anticipate that insight into the molecular mechanisms of mTOR-mediated axonal outgrowth will identify potentially novel drug targets for SCI (e.g. GRP). More importantly, we believe that these studies will lead to the development of new strategies to repair damaged nerve fibers and improve functional recovery of SCI patients.

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**Neeraja Syed – Principal Investigator**
Rutgers, The State University of New Jersey – Biological Sciences
Grant Award: $60,000

Project Title: *Promoting Myelination on Adult Axon by Soluble Neuregulin-1*

Spinal cord injury (SCI) is a complex and devastating injury with a very little chance of functional recovery. Although the spinal cord is protected by hard bones of the spinal column, severe injury leads to paralysis. In the United States, approximately, 12,000 people are victim to SCIs each year and a quarter of a million people are living with them. The injured axon loses its myelin sheath, which is a cellular structure formed by myelin-forming cells and is important for rapid saltatory nerve conduction. The primary goal of spinal cord injury research is to find a way to regenerate damaged axons and rebuild the myelin to provide complete functional recovery to injured patients. It is imperative that novel approaches to SCI repair have to be explored. Among many strategies, experimental transplantation of myelin-forming cells such as Schwann cells and oligodendrocytes have proven to facilitate the rebuilding of myelin sheath on damaged axons thus helping them to regenerate. This provides the possibility of isolating Schwann cells from the patient's peripheral nerve and transplanting them at the lesion site to improve repair of damaged axons and eventually the functional recovery. However, the ability of Schwann cells to rebuild myelin on adult axon is limited: myelin segments formed by transplanted Schwann cells are thinner and shorter than the normal segments formed during development and covers less than 50% of the demyelinated area, leaving behind intermittent areas of naked axons. Therefore, a therapeutic strategy to enhance the myelination capacity of Schwann cell is necessary to improve remyelination and repair of damaged axons following nerve injury.

The remyelination defect on adult axon is common to both the Central Nervous System (CNS) and the Peripheral Nervous System (PNS): Schwann cells also fail to fully remyelinate regenerating axons of the PNS. This suggests that perhaps in adult animals, the mature axons either prevent Schwann cells from completing remyelination or do not provide sufficient amount of "pro-myelinating" signal to the associated Schwann cells. Recently, it has been shown that neuregulin1-type III (Nrg1-type III), a growth factor expressed on axonal membrane, is crucial for promoting myelination by the associated Schwann cells. My preliminary data shows that the expression level of Nrg1-type III was drastically lower in adult axons, suggesting the lack of necessary pro-myelinating signal transmitted to the Schwann cells. My data also shows that Nrg1-Type III provided in a soluble form enhances the myelination capacity of Schwann cells. Based on these findings, I hypothesize that the myelination defect on adult axon is due to the low levels of Nrg1-type III and the myelination could be improved by treatment with soluble Nrg1-type III. To test the hypothesis, I will first compare the Nrg1-erbB signaling function of embryonic and adult axons in Schwann cells. Second, I will determine whether soluble Nrg1-type III improves myelination on adult axons. Finally, I will determine whether systemic injection of soluble Nrg1-type III improves myelination on regenerating axons in an animal model. Results from this study will provide insights into developing a therapeutic strategy using soluble Nrg1-Type III to rebuild myelin on damaged lesions of the CNS, which will benefit patients with spinal cord injury by facilitating regeneration of injured neurons.

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