DIRECTORY OF GRANT AWARDS
2011 GRANT CYCLE

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

2011 GRANT CYCLE

DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

JUNE 2011

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 2011 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.

2011 MEMBERSHIP INFORMATION

Susan P. Howley, Chairperson
Peter W. Carmel, M.D.
Robin L. Davis, Ph.D.
John D. Del Colle
Cynthia Kirchner, M.P.H.

COMMISSION PERSONNEL

Christine Traynor, Administrator
Mary Ray, Fiscal Manager

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

Monica Driscoll, Ph.D.
Rutgers, The State University of NJ
$589,000

Project Title: *Molecular Mechanisms of In-Vivo Neuronal Regeneration & Reconnection*

In spinal cord injury axons are often sheared, causing a loss of neuronal connectivity and impaired neurological function. The rapid regeneration of severed neurons is an obvious goal for the treatment of spinal cord injury. Future repair substrates may be surviving severed neurons or introduced neuronal progenitor cells. Unfortunately, knowledge of molecular mechanisms that actively promote neuronal regrowth and reconnection in the living animal is limited. Thus, detailed deciphering of molecular mechanisms that promote neural repair within physiological context will be essential for any successful strategy for combating the incapacitating consequences of SCI.

The central goal of our work is to increase the understanding of the molecules that promote regeneration of injured neurons. To accomplish this, we exploit the powerful C. elegans model system, which offers unique experimental advantages. C. elegans is a simple invertebrate nematode that has only 959 cells in its transparent body. The entire nervous system is made up of 302 identified neurons. We can visualize fluorescently labeled neurons in the transparent body; induce single axon breaks using a laser, and monitor regeneration of injured neurons in the living animal. In addition, C. elegans is easily genetically manipulated--all the genes are cataloged and we can systematically reduce the activity of each one to test its role in regeneration and reconnection. Since most basic biological processes are conserved from C. elegans to humans, this unique model system should provide novel insight into the mechanisms regulating neuronal regeneration and repair in humans.

Our previous work led to the surprising discovery that the cell death proteins CED-3 (caspase protease) and CED-4 (activator of CED-3) are important for early regeneration events following laser axotomy. We also find that the calcium-storing protein calreticulin (CRT-1) is important for the normal localized calcium change that occurs following axotomy and appears to function in the same regeneration pathway as CED-3 and CED-4. Our working hypothesis for the novel CED/CRT regeneration pathway is that axotomy induces calcium influx into the neuron and CED-4 binds this free calcium, enabling it to locally activate CED-3 caspase to promote axonal regeneration. Interestingly, CED-3 caspase also influences how rapidly the regrowing injured neuron can reconnect to repair the severed neuron. We will define molecules, and their biological activities, that influence early events in neuronal regeneration:

Aim 1. We will use state-of-the-art analysis tools to follow and quantitate outgrowth, reconnection and calcium flux properties in injured neurons mutant for CED-3, CED-4,

and CRT-1. We will also determine the order in which these proteins work in the regrowth initiation mechanism.

Aim 2. We will manipulate specific parts of the CED-4 protein that may bind calcium or that are known to promote self-association or activating association with CED-3 to test our proposed model for regeneration initiation in which CED-4 senses calcium and in turn activates CED-3.

Aim 3. We will examine the relationship of the CED/CRT pathway to other proteins known to influence in vivo regeneration in C. elegans. This work should define the genetic pathways that are involved in initiating regeneration in injured neurons.

Aim 4. We will focus on novel gene discovery for the process by which local calcium elevation activates new growth cone outgrowth. We will reduce the activity of each of 191 candidate calcium-binding proteins to identify potential players in this process. We expect work will identify conserved initiators of regenerative outgrowth.

Study of pathways operative in regeneration initiation and reconnection using unique approaches in a genetic model should contribute significant advances toward the elaboration of basic molecular mechanisms of neuronal repair that should ultimately suggest novel therapeutic approaches.

Contact Information:

Monica Driscoll, Ph.D.
Rutgers, The State University of NJ
Dept. Cell Biology & Neuroscience
604 Allison Road
Piscataway, NJ 08854
732-445-7182
driscoll@biology.rutgers.edu

Tracy Tran, Ph.D.
Rutgers, The State University of NJ
$599,880

Project Title: *Molecular Mechanisms that Control the Long-Range Pathfinding of Dorsal & Ventral Spinal Commissural Axons in the Developing CNS*

Spinal cord injuries cause damage to important nerve fiber tracts by severing connections between axons (thin processes extended by neurons that transmit information) and their target cells that ultimately leads to the loss of both sensory and motor functions in patients. During neural development and following injury, newly formed and regenerating, respectively, axons are led along appropriate pathways to their functional targets by molecular cues present in their environments. Therefore, it is critical to identify the molecular mechanisms underlying axon guidance in order to design suitable treatments for promoting the regeneration of axon tracts damaged by spinal cord injury.

Recent studies have shown that spinal commissural neurons, which extend axons across the midline from one side of the spinal cord to the other, and then project to the brain, represent components of important ascending axon tracts, which convey external sensory information (touch, pain and body position) to higher brain centers. However, the precise paths followed by different classes of commissural axons as they extend to the appropriate target cells in the brain are not known. Moreover, very little is known about the molecules that guide these axons to their appropriate targets.

Therefore, we propose to trace the trajectories of multiple classes of ascending spinal commissural axons, in both chick and mouse embryos, and to identify the molecules and understand the guidance mechanisms that these axons use to find their targets. The proposed studies will be carried out in whole embryos using molecular genetic techniques to label particular subsets of spinal commissural axons and to manipulate a variety of candidate guidance molecules. Interestingly, many of the molecules that regulate axon guidance during development are also present in the adult nervous system. Accumulating evidence indicates that the levels of these molecules are dramatically altered after spinal cord injury, which could underlie the inability of the spinal cord to regenerate following injury. Thus, our proposed studies on how spinal commissural axons are guided to the brain during normal development should not only significantly contribute to our understanding of the molecular mechanisms governing the formation of specific neuronal connections, but also suggest new approaches for the design of therapeutic strategies aimed at regenerating the injured spinal cord.

Contact Information:

Tracy Tran, Ph.D.
Rutgers, The State University of NJ
Dept. Biological Sciences
225 University Ave.
LSC 601D
Newark, NJ 07102
973-353-5542
tstran@andromeda.rutgers.edu

Randall McKinnon, Ph.D.
UMDNJ-RWJMS
$552,720

Project Title: *Reprogramming Fibroblasts to OPCs for SCI Repair*

We will pioneer a strategy to reprogram somatic fibroblasts into patient-specific neural stem/progenitor cells for transplant therapy and spinal cord repair. The rational for this research program is as follows. Traumatic spinal cord injury destroys neurons and supporting glia. The axons of damaged neurons do not regenerate, and lost neurons and their supporting glial cells are not replaced. There is currently no clinical therapy that improves long term outcome.

In contrast, animal model studies have demonstrated significant functional recovery from injury with exogenous transplants of glial cells. Recently, we found that cell transplants into mice can completely rescue lost motor function and early death of a brain glial cell deficit. These pre-clinical studies have now progressed to clinical trials to evaluate safety and proof of principle for grafts of glial cells derived from human embryonic stem cells. This is a very important trial that will examine safety and effectiveness of such cells. However, our recent studies also raise grave safety concerns (tumor formation) for stem cell derived grafts. To move forward this field needs a source of glial cells that are tissue compatible, ethically acceptable and non-tumorgenic. The reprogramming field is taking us in the right direction with strategies to generate patient-specific induced stem cells from adult skin fibroblasts. While these are tissue compatible and ethically acceptable, they are also equivalent to embryonic stem cells in their tumor potential. Our studies will circumvent these concerns by building on iPS technology to directly induce neural progenitors from skin cells. We will focus on the induction of oligodendrocyte progenitor cells, the glial progenitor which in pre-clinical studies promotes repair and recovery in spinal cord injury. We will use combinations of chromatin remodeling factors and specification genes to generate these cells from fibroblasts, and we will identify the key genes required. Our strategy can be applied for the genesis of any progenitor cell type from fibroblasts, and our aims will move the field of transplant biology forward toward rational approaches for clinical therapeutics and regenerative medicine.

Contact Information:

Randall McKinnon, Ph.D.
UMDNJ-RWJMS
Department of Surgery
675 Hoes Lane, S-225
Piscataway, NJ 08854
732 235-4419
mckinnon@umdn.edu

EXPLORATORY RESEARCH GRANT RECIPIENT:

Richard W. Padgett, Ph.D.
Rutgers, The State University of NJ
$199,279

Project Title: *Studies of the MicroRNA Bantam and Glial Proliferation*

Long-term goals: This proposal seeks to understand the mechanisms by which a microRNA bantam affects the proliferation of glial cells. An intensively studied area of glia biology is its potential role in treatment of spinal cord injuries. These injuries are mechanical injuries that result in damage at a particular site, followed by the subsequent loss of adjacent neurons and glia. Strategies are needed to promote axonal remodeling and glial cells are a key aspect of nerve growth.

Preliminary findings: In preliminary work, my lab found that bantam regulates the proliferation of glial cells in Drosophila. Since bantam is conserved in humans, we tested the hypothesis that the two human homologs affect the growth rate of glioblastoma cell lines. We found that increasing bantam increases cell number, while inhibiting endogenous bantam reduces cell growth, indicating a conserved function for bantam.

MicroRNAs can be used in therapies: microRNA control of genes is an intense area of investigation, as it appears that the majority of genes are regulated to some degree by one or more miRNAs. Given their novel molecular structure, miRNAs are becoming a focus of future therapies and may provide a novel avenue to control gene pathways. Some early successes toward this strategy have already been obtained. Of particular note is the observation that many miRNAs are active in neural tissues. Many miRNAs have been shown to be regulated in glia, and of the thousand or so miRNAs in humans, a few have been shown to regulate different aspects of glia differentiation or proliferation. Of these, a few are conserved in Drosophila (e.g., miR-137, miR-451, miR-29b, miR-125, let-7, miR-128, miR-34a, and miR-125b). Some of these have been associated with expression in nervous tissue, but to our knowledge, none have been shown to affect glial cell proliferation in both organisms. This argues that bantam is unique and provides an impetus to study it further. We do not expect that bantam will be a perfect therapeutic by itself, but in combination with other genes, it may provide a more comprehensive approach toward controlling growth of damaged nervous tissue.

Glial control axonal remodeling: Glial cells are essential for many neuronal functions. Not only do they provide support for neurons, but also they are necessary for neuronal survival and provide guidance for axons. Understanding how glial cell proliferation is controlled is an important area of investigation. If these cellular functions could be better understood, they could provide important therapeutic avenues for inducing glial cell growth aimed at spinal cord repair.

Proposed studies: A number of well-established Drosophila techniques will be used to investigate how bantam controls glial cell proliferation and subsequently these findings will be applied to human glial cells. In Aim #1, the molecular and developmental mechanisms by which bantam changes glial cell number will be investigated. In Aim #2, novel abdominal transplantation techniques in Drosophila will be used to culture brain

sections from transformed flies to quantitate the proliferative and invasive potential of newly induced glia. In Aim #3, the mechanism by which the two human bantam homologs regulate proliferation of glioblastomas will be investigated. Bantam is in a very small group of miRNAs that have maintained conserved, evolutionary functions in glial proliferation. Therefore, the study of bantam represents a unique opportunity to study this process in detail in Drosophila and apply those findings to mammalian experiments.

Contact Information:

Richard W. Padgett, Ph.D.
Rutgers, The State University of NJ
Waksman Institute of Microbiology
190 Frelinghuysen Road
Piscataway, NJ 08854
732-445-0251
padgett@waksman.rutgers.edu

FELLOWSHIP GRANT RECIPIENTS:

Olivier Mauti, Ph.D.
Princeton University
$150,000

Project Title: *Investigation of Cell-Cell Signaling in Spinal Neurogenesis*

Spinal cord injuries (SCI) typically cause life-long physical disabilities with devastating consequences for patients and their families. Generation of new functional neurons represents a promising treatment for restoring spinal cord function. One of the many challenges for researchers is obtaining cells in large quantities that can replace damaged neurons. Since there are no spare neurons in the human body that can be used for transplantation, researchers have taken advantage of embryonic stem cells (ESCs) that can be transformed into neurons followed by implantation into the lesion site. This approach has provided some promising results for improving spinal cord function in animal SCI models. Alternative approaches for restoration of neural function involve inducing endogenous neural progenitors present in the adult spinal cord to generate new neurons in their normal environment. Nevertheless, there are drawbacks associated with either approach that must be addressed by augmenting or optimizing the methods currently used.

The goal of this study is to improve our understanding of the complex molecular mechanisms that control neural progenitor proliferation and their differentiation into neurons so they may be better used to optimize existing technologies for the treatment of SCI.

Contact Information:
Olivier Mauti, Ph.D.
Princeton University
Washington Road, LTL 113
Princeton, NJ 08544
609-258-2914
omauti@princeton.edu

Aaron Carlson
Rutgers, The State University of NJ
Dept. Biomedical Engineering
$60,000

Project Title: *Bioactive Scaffolds & hESC-Derived Neurons for Treating SCI*

New sources of human neuronal cells, including those derived from human embryonic stem cells (hESCs), have brought the goal of neuronal transplantation to treat spinal cord injury (SCI) closer to reality. Both neural stem cells (hESC-NSCs) and mature neurons derived from hESCs have been transplanted into the injured spinal cord, but survival and continued neuronal differentiation has been limited. This is partially due to the environment in the post-injury spinal cord strongly favoring glial differentiation and inhibiting neuronal differentiation of uncommitted multipotential neural cells, highlighting the importance of transplanting committed neuronal cells rather than multipotent progenitors. In addition, it is difficult to differentiate hESC-derived cells to mature neuronal cells in vitro without needing to detach cells from the culture substrate before transplantation, which results in a great deal of cell death.

To address these challenges, we propose to take a tissue engineering approach and develop a single system that can be used to differentiate hESC-NSCs in vitro, transplant neuronal cells derived from hESC-NSCs into the injured spinal cord, and promote survival and integration of transplanted neuronal cells within the spinal cord by delivering trophic factors. To achieve this, we will incorporate neurotrophic factors (NTFs) that promote neuronal survival and maturation into fibrous polymer scaffolds, and examine the combined role of fibrous architecture and sustained release of NTFs on neuronal differentiation and maturation in vitro and on neuronal survival and integration in vivo. Our hypothesis is that fibrous architecture and local release of NTFs will enhance neuronal differentiation and maturation of hESC-derived neural stem cells (hESC-NSCs) in vitro relative to cells differentiated on 2-D substrates or 3-D substrates in the absence of released NTFs. Further, we hypothesize that NTF-releasing scaffolds will promote enhanced survival and integration of transplanted neuronal cells in the injured spinal cord compared to cells delivered by injection or by scaffolds without NTFs. The outcome of this research will provide insights into the role of the combined effects of fibrous architecture and NTF release on in vitro and in vivo behavior of neuronal cells derived from hESC-NSCs. Additionally, successful integration of hESC-derived neurons into the spinal cord will demonstrate that fibrous, NTF-releasing scaffolds are a promising platform for delivering differentiated neuronal subtypes to the spinal cord to achieve specific functional endpoints, including improvement of motor function or management of neuropathic pain.

Contact Information:

Aaron Carlson
Rutgers, The State University of NJ
Dept. Biomedical Engineering
599 Taylor Road
Piscataway, NJ 08854
732-239-6379
carlsoal@eden.rutgers.edu

Yi Guo
NJ Institute of Technology
$60,000

Project Title: *Characterizing Motor Control Signals in the Spinal Cord*

In order to improve the quality of life for individuals with spinal cord injury (SCI), medical, neuroscience and engineering researchers have sought to understand the ways in which a person's movement intentions are planned, transmitted and result in muscular activity.

In the past, rehabilitation engineers have designed assistive technologies that include voice input for typing and wheelchair control, and head, tongue and shoulder movements to use joysticks for electric wheelchairs and robot arms. While such systems are useful, they do not restore full function to the person. Since an SCI damages or severs the spinal cord in a limited region along its length, the portion of the spinal cord and the nerves connecting to the muscles remain largely intact, but lack driving signals. Neural engineers have attempted to make use of this healthy circuitry by providing artificial; computer generated driving signals to stimulate the muscles into productive use. Similarly, as the brain and spinal cord above the damaged area are also intact, other neural engineering groups have sought to detect the individual's intentions by recording brain signals using electrodes placed on the surface of the head, or implanted in the neural tissue of the brain. This approach is referred to as brain-computer interface (BCI).

This proposed study will generate a new understanding of how the neural signals of the spinal cord that communicate the brain's intentions to the muscles represent the actual movement of the limbs, with the intention of eventually improving the performance of spinal and muscle stimulation. To date, BCI studies have not found a correspondence between actual movements parameters and neural signals. This is most likely because many areas of the brain contribute to limb control and that the neural activity in any one local region may not correspond to the limb's position or muscle forces. Thus, with most BCI signals, there is a mismatch with the signals expected by the muscles. This project expects that the distributed signals in the brain converge on the spinal cord and the signals recorded from the spinal cord may take on a closer representation of the actual movement.

Despite years of research, the neural engineering and neuroscience communities continue to debate whether the signals reaching the muscles encode force or position. One argument is that movements require such complex patterns of muscle force that these patterns must be computed in the brain based in an internal model of the person's limbs and the environment. The competing theory proposes that the brain's intentions are coded as rather simple intended joint or limb trajectories in the spinal cord, and that these trajectories are used by reflex circuits that connect the spinal cord to the muscles to generate the muscle forces.

This project will record spinal signals of animals (rats) and compare them to the limb positions and forces produced by the animal when pushing a lever to obtain food. This comparison as well as the examination of how the animal responds to unexpected pushes on its arm during its routine arm movement will help determine if force or position is

contained in the signal. Knowledge of what parameters are encoded will be very useful in assessing the eventual restoration of function, through spinal cord repair, and improving the performance of functional electrical stimulation or neural prostheses by providing a more physiologically correct driving signal to the muscles.

Contact Information:

Yi Guo
NJ Institute of Technology
Dept. Biomedical Engineering
323 Martin Luther King, Jr. Blvd.
Newark, NJ 07102
973-596-3335
yg9@njit.edu

Kamana Misra, Ph.D.
UMDNJ-RWJMS
$150,000

Project Title: *BMP Signaling in V2Interneuron and Motorneuron Development*

The adult spinal cord (SC) is wired in such a way that each part performs a distinct and specialized function. The dorsal SC is mostly involved in processing sensory inputs while the ventral part is involved in giving a motor response to the sensory signal received. The distinction of the SC into dorsal and ventral regions is therefore essential for its functioning. V2 interneurons (INs) are one such class of INs that are specified in the ventral spinal cord and emerge from progenitor domain neighboring the spinal motor neurons (MNs). Proximity to MNs and examples of interconversion between these neighboring fates suggest an important role for these INs in modifying motor functions in the spinal cord. Consistently, V2 INs modify the progression of MN disease amyotrophic lateral sclerosis (ALS) in transgenic mice. V2 INs also form the core neuronal elements of the locomotor central pattern generators (CPGs) that can endogenously produce rhythmic patterned outputs in spinal cord. V2 INs therefore have multiple roles in context to spinal cord function. However, very little is known about contributions of V2INs to adult circuits and even lesser for directed differentiation of stem cells into V2 INs.

The studies outlined in this proposal will address novel molecular mechanisms involved in generating V2INs. Since MNs and V2INs arise from neighboring progenitor domains, these studies will also provide important insights into mechanisms involved in segregating these two fates. Furthermore, the directed differentiation of stem cells into V2 INs will be directly relevant to the development of therapeutic approaches following SCI and other diseases of SC.

Contact Information:

Kamana Misra, Ph.D.
UMDNJ-RWJMS
Dept. Cell Biology & Neuroscience
679 Hoes Lane, CABM
Piscataway, NJ 08854
732-235-4442
misrakp@umdnj.edu