NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

2005 B CYCLE

DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

DECEMBER 2004

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 2004 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, 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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INDIVIDUAL RESEARCH GRANT RECIPIENTS

PRINCIPAL INVESTIGATOR – Christopher Rongo, Ph.D.
Basic Science Proposal
Grant Number 05B-005-SCR1
Grant Award $191,712

Project Title: The Role of Notch/LIN-12 in Glutamate Receptor Signaling and Excitotoxic Neuronal Damage

The goal of this proposal is to test whether Notch/LIN-12 signaling molecules play a role in glutamate-mediated neuronal death. Spinal cord injury is a distressing illness that results in the loss of sensory and motor function. Affected individuals often experience, with varying degrees, the loss of mobility, sensation and autonomic function, and often experience chronic neuropathic pain. The key cells that are damaged by spinal cord injury are neurons, and this damage can result from mechanical damage (e.g., traumatic injury) or ischemia (oxygen deprivation) caused by breakdowns or obstructions in the blood vessels that supply the spinal neurons. The initial events of the spinal cord injury are often restricted to a small region of neurons in the spinal cord. However, this early damage event results in the release of large quantities of the neurotransmitter glutamate at the initial damage site. This massive release of glutamate leads to a build up of glutamate in the secondary tissues that surround the initial injury site. Whereas low levels of glutamate are used by neurons as chemical signals that shuttle back and forth between neurons, high levels of glutamate caused by injury instead over activate glutamate receptors on secondary site neurons, resulting in the excessive depolarization of these cells, calcium influx, and subsequent death of the neurons. Dying secondary neurons often release their own stores of glutamate, leading to yet more glutamate accumulation and waves of dying neurons spreading out from injury site.

The identification of drugs that block or delay glutamate receptor activation would significantly limit receptor-induced damage that results from spinal cord injury. One of the primary ways by which neurons regulate glutamate receptor activity is by regulating the amount of these receptors that reach the surface of neurons. This proposal aims to identify important proteins that regulate the movement of glutamate receptors to the surface of neurons using a genetic approach in the nematode C. elegans. C.elegans use glutamate receptors in the sensory circuits that are strikingly similar to the sensory circuits that are found in the spinal cord. My lab previously showed that these receptors are localized to the surface of the neuron, and we have been identifying C. elegans genes that regulate the movement of these receptors. The over activation of these same glutamate receptors in C. elegans leads to excitotoxic neural death. Our preliminary results suggest that a protein called LIN-12 regulates the movement of glutamate receptors to the neuron surface. This proposal contains three aims for understanding the role of LIN-12 signaling in this process. First, we will determine what other proteins help LIN-12 regulate the movement of glutamate receptors. Second, we will determine whether LIN-12 works in neurons or in the cells that support neuron function. Finally, we will test whether mutants in LIN-12 or other proteins that we discover can decrease neuronal death in an existing model of glutamate-mediated neuronal death in C. elegans that is similar to the glutamate-mediated toxicity that follows an initial spinal cord injury. We hypothesize that LIN-12 and its partner proteins help facilitate the glutamate–mediated toxicity observed during the critical period that follows an initial spinal cord injury. By identifying and characterizing these proteins, this work should identify key targets for new therapeutic interventions that limit neuronal damage following spinal cord injury. Researchers have previously used C. elegans as the foundation for understanding the process of cell death, extrapolating their findings to the corresponding human genes; indeed, the Nobel Prize in Physiology & Medicine for 2002 celebrated these achievements. Of the five genes that my lab has discovered to be playing a role in glutamate receptor biology so far, all five have human equivalent genes playing a similar or identical role, suggesting that our findings in C. elegans are likely to be applicable to human health.

Contact Information:
Christopher Rongo, Ph.D.
Waksman Institute of Microbiology, Department of Genetics
Rutgers, The State University of New Jersey
190 Frelinghuysen Road
Piscataway, New Jersey 08854-8020
732-445-0954

PRINCIPAL INVESTIGATOR – Mengqing Xiang, Associate Professor
Basic Science Proposal
Grant Number 05B-007-SCR1
Grant Award $400,000

Project Title: Role of Foxn4 in Spinal Cord Development and Regeneration

Spinal cord injury, currently without any effective treatment, presents an enormous medical, public health and economic problem. Thanks to recent advances in the study of neural stem cells, the previously inconceivable regeneration of the damaged spinal cord is within the reach of reality. 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 stem cells. Such an approach has been successfully applied in rodent models of spinal cord injury to achieve some neural regeneration which restores limited sensory and motor functions. To improve further on this exceptionally promising approach to develop it as a viable therapy, however, it is a prerequisite to understand the development and genetic programs that direct the proliferation, specification and differentiation of stem cells. Since the differentiation of stem cells normally recapitulates the events that occur during embryogenesis, the study of the molecular basis governing spinal cord development is important for the future success of stem cell mediated regeneration.

The goal of this proposal is to understand the molecular events that control the specification and differentiation of sensory and motor neurons during development and regeneration of the spinal cord. This application will focus on the role of an important transcription factor, which displays several salient features implicating it as a putative regulator for fate specification and/or early differentiation of a distinct spinal sensory neuron subtype. 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 regeneration of desired sensory neurons in the chick system. The knowledge gained from these studies may help to identify novel molecular targets that can be used to promote functional reconstruction of neuronal circuits in the injured spinal cord.

Contact Information:
Mengqing Xiang, Associate Professor
Center for Advanced Biotechnology & Medicine
UMDNJ-Robert Wood Johnson Medical School
675 Hoes Lane, 2nd Floor, RM 240
Piscataway, New Jersey 08854
732-235-4491

PRINCIPAL INVESTIGATOR – Michael P. Matise, Ph.D.
Basic Science Proposal
Grant Number 05B-011-SCR1
Grant Award $400,000

Project Title: Molecular Control of Spinal Cord Neuronal Progenitor Differentiation

The long-term goal of this proposal is to improve the success of stem cell replacement therapies to treating spinal cord injury (SCI) by characterizing the activity of an important regulator of neurogenesis in the embryonic spinal cord. Some of the most exciting strategies for restoring function following SCI involve therapies that seek to employ immature "stem cells" to replace the function of cells that are lost as a consequence of the trauma. Much attention has been focused on isolating and characterizing stem cells that can, when transplanted into the CNS, develop into fully functioning neurons. While promising, to date the success of these approaches has been limited, perhaps due to the fact that the adult spinal cord does not present a conducive environment for the formation of neurons from immature cells. Furthermore, most current studies focus primarily on the ability of transplanted cells to adopt a "generic" neuronal identity. However, the mature spinal cord is composed of hundreds of distinct neuronal cell classes that are generated exclusively during embryonic development. Therefore, in order to restore even partial function, transplanted stem cells must do much more than simply differentiate into a neuron with an unspecified identity, but rather must generate at a minimum the types of neurons that comprise the circuitry controlling movement and sensation.

Neuronal stem cells possess the potential to generate the wide array of cell types that normally exist in the adult spinal cord. These cells are essentially specialized versions of normal spinal cord progenitor cells found in the developing embryo. Their utility as a therapeutic tool depends on preserving their full potential in vivo in adult injury sites, and understanding the steps that normal progenitor cells must undergo to generate neurons is critical to the success of this approach. The cell-cycle regulators being investigated in this proposal play a central role in regulating the transition of multi-potent progenitors into newly-born neurons with distinct phenotypic properties in the developing spinal cord, and are likely to be critically involved in this success of such SCI treatment strategies.

In the experiments described in this grant proposal, we will investigate the function of a key regulator of neurogenesis. We believe this factor, p57kip2, plays a central role in controlling the generation of neurons from multi-potent neuronal stem cells by regulating two important steps in this transition. Our experiments will make use of well-established vertebrate animal model systems for studying spinal cord development. These systems permit us to perform a variety of experimental manipulations that will allow us to define the function of p57 protein in the spinal cord.

We expect that it will be feasible to extend our basic work in the near future to studies that will directly examine the role of cell-cycle/neurogenesis regulators in controlling the formation of functional neurons from experimental stem cells in vitro and in vivo.

Contact Information:
Michael P. Matise, Ph.D., Assistant Professor
Department of Neuroscience & Cell Biology
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
675 Hoes Lane
Piscataway, New Jersey 08854
732-235-3471

PRINCIPAL INVESTIGATOR – Noshir A Langrana, Ph.D.
Basic Science Proposal
Grant Number 05B-012-SCR1
Grant Award $150,000 – One Year Grant

Project Title: Bifunctional Biomaterial Design for Spinal Cord Regeneration

This proposed research addresses fundamental issues in enhancing axon regeneration following spinal cord trauma, which is the first listed objective in the NJCSCR guidelines. The broad, long term objective of this research is to develop biomaterials that spur regeneration of the spinal cord. Two general tissue engineering strategies have been employed in attempts to restore spinal cord function following trauma. The first and most prevalent is the development of biomaterials that serve as scaffolds to stimulate axons to regenerate and grow through the injury site. The second strategy is to employ mechanical force, or traction, to axons at very slow rates and physically force the nerves to grow, just as the spinal cord lengthens as we mature from infants to adults. The second technique has been used in vitro to generate neural tissue in hope to ultimately "splice" together the spinal cord. We have developed a novel biomaterial that will ultimately enable us to apply both strategies of spinal cord regeneration in vivo. The biomaterial is a polyacrylamide hydrogel that can be reversibly crosslinked with DNA strands to change its stiffness and apply force. When crosslinks are introduced, the hydrogel shrinks, and, if attached to an object, exert force on that object. Moreover, the biomaterial backbone can also be functionalized with extracellular matrix molecules to support axon attachment and growth. Thus, we believe that our DNA-crosslinked gels will induce spinal cord regeneration via two important mechanisms. To our knowledge, this dual modality has not been tried.

The goal of this proposal is to optimize the characteristics of the biomaterial and DNA delivery to induce axon regeneration through the hydrogel scaffold and physically stretch and reconnect the spinal cord. The specific aims of this proposal are: (1) To identify the force-actuating potential of DNA-crosslinked hydrogels; (2) To functionalize DNA-crosslinked hydrogels for axon growth in vitro. Following completion of these aims, we will have demonstrated the capacity of our novel hydrogels to stimulate axon regeneration by the two distinct mechanisms. We plan to proceed to animal studies to evaluate the efficacy of the hydrogels in vivo, and to investigate modifying other acryl-based polymers, such as poly-methyl methacrylate to enhance our biomaterial library for spinal cord regeneration.

Contact Information:
Noshir A. Langrana, Ph.D., Professor
Department of Mechanical & Aerospace Engineering
& Biomedical Engineering
Rutgers, The State University of New Jersey
Busch Campus Engineering Bldg, RM B232
98 Brett Road
Piscataway, New Jersey 08854
732-445-3618

PRINCIPAL INVESTIGATOR – Renping Zhou, Ph.D.
Basic Science Proposal
Grant Number 05B-013-SCR1
Grant Award $397,888

Project Title: Roles of Ephrin-A5 in Spinal Cord Development

Spinal cord injury is a major cause of disability. Extensive clinical and experimental studies showed that traumatic spinal cord injury results in loss of neurons and nerve pathways, which lead to partial disability or complete paralysis. Recent advances in the research of stem cells, a type of cells capable of producing different types of tissues, hold the promise that one day, replacement of lost spinal cord neurons with stem cells may lead to complete recovery of spinal cord injuries. However, a major challenge of stem cell therapy will be the rewiring of the transplanted neurons, connecting them into functional spinal neural circuits. Although considerable advances have been made in the understanding of the molecular signals that help to guide the nerve fibers, in general using invertebrate model systems such as fruit flies and nematodes, much remains unknown about how the vertebrate spinal cord neural circuits are constructed and what are the molecules that regulate this process. Our long term objective is to identify molecules that contribute to the construction of functional spinal cord neural circuits, in the hope that this information will be used in future cell replacement therapies for spinal cord injuries.

The preliminary studies conducted in our laboratories showed that two molecules, named ephrin-A5 and EphA5, might play important roles in the construction of spinal cord neural circuits. These two molecules are located on the membranes that wrap around the cells and they talk to each other by physically forming a complex, eliciting biochemical changes within the cells. It has been shown in our previous analysis that ephrin-A5; a known repulsive signal for nerve fibers is localized in spinal cord regions where the spinal cord nerve fibers avoid. It is hypothesized that ephrin-A5 functions to prevent spinal cord nerves from traveling to this region, and thus playing critical roles in organizing the spinal nerves. To test this hypothesis, experiments are proposed to study localization of ephrin-A5 and its receptor EphA5 proteins during development of spinal cord neural circuits, using techniques that will reveal the presence of these proteins. Since the spinal cord is made of many different cell types, it will be determined in which cell types they are located. The functions of ephrin-A5 and EphA5 will be further studied using a well-established spinal cord tissue culture method in an incubator. Artificially generated mutant molecules that block the functions will be added to the cultured spinal cord tissues to examine effects on the organization of spinal cord nerve pathways. And finally, mice deficient for ephrin-A5 and EphA5 genes, alone or in combination, will be examined using techniques that trace nerve fibers to identify defects in spinal cord organizations. These studies together will provide a critical assessment of roles of this molecular pair in the development of spinal cord.

Understanding how the spinal cord nerve fibers are organized will help to design interventions to properly reconnect spinal cord nerve fibers in future stem cell therapy or other regenerative therapies. Spinal cord injury patients in New Jersey and elsewhere will all benefit from these therapeutic advances.

Contact Information:
Renping Zhou, Ph.D., Professor
Department of Chemical Biology
Ernest Mario School of Pharmacy
Rutgers, The State University of New Jersey
164 Frelinghuysen Road
Piscataway, New Jersey 08854
732-445-3400 X264

PRINCIPAL INVESTIGATOR – William G. Wadsworth, Ph.D.
Basic Science Proposal
Grant Number 05B-015-SCR1
Grant Award $315,204

Project Title: Molecular Mechanisms of Axon Guidance

This proposal intends to research genetic study to explore the molecular mechanisms that guide axons back to their targets following injury. Following injury, regenerating axons must be guided back to their targets in order for the proper connections to be re-established. Several of the molecules that are involved in axon guidance were first discovered in the model organism C. elegans, a nematode. The same molecules that function to guide axons in the simple nematode nervous system also guide axons in the complex human nervous system. They are present in the adult nervous system and recent studies indicate that their expression changes during injury, which could have a profound influence on the ability of regenerating neurons to find their proper targets and form functional circuits. Using the powerful genetic techniques available in C. elegans, other molecules that interact with the guidance molecules and that are required for their function are being sought.

The discovery of new molecules involved in axon guidance and a better understanding of the molecular mechanisms of axon guidance could lead to new therapies aimed at directing regenerating axons towards their proper targets

Contact Information:
William G. Wadsworth, Ph.D.
Department of Pathology & Laboratory Medicine
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
675 Hoes Lane, Room R228, 2nd Floor
Piscataway, New Jersey 08854
732-235-5768

PRINCIPAL INVESTIGATOR – Ron Weiss, Ph.D.
Basic Science Proposal
Grant Number 05B-017-SCR1
Grant Award $391,189

Project Title: Programmed Tissue Engineering for Spinal Cord Regeneration

This project will focus on building synthetic gene networks that precisely control stem cell differentiation. Spinal cord injury is a major cause of paralytic disabilities. Currently, there are no effective therapies that result in significant alleviation of such disabilities. The therapies that are in use are generally limited to preventing more extensive accumulation of tissue damage. No effective therapies can reverse spinal damage through the regeneration, or re-growth of new cells. Several experimental studies suggest that transplantation of undamaged cells into the site of injury may eventually be an effective avenue for therapeutic intervention. While encouraging, such therapies are inherently limited by a lack of suitable transplantable material that will fully regenerate the spinal cord without complications such as tissue rejection. Recently, it has been suggested that stem cell populations, whether from embryonic or adult tissue sources, may represent a source of transplantable material for therapeutic tissue repair. Stem cells are cells that can generate many types of mature cell populations for lifelong time periods. The major barrier to realizing the potential of stem cells is to devise ways to direct these cells toward different pathways of mature tissue or cell production. That is, for spinal cord repair it is necessary to ensure the production of the nerve and associated cells that are normally found in this tissue. It will also be necessary to ensure that the mature cells are produced in the proper amounts and in an appropriate three-dimensional tissue structure. The mechanisms that control the production of mature cells from stem cells in normal fetal or adult physiological contexts are poorly understood. Nevertheless, a number of molecules that function as genetic "master switches" in stem cells to direct the production of different cell types have been identified.

We propose to harness these "master switches" by implementing them in artificially controlled regulatory circuits constructed inside stem cells by genetic engineering. In this way it will be possible to trigger the controlled production of different mature cell populations after transplantation of the genetically modified stem sells into the site of tissue injury. In addition, it will eventually be possible to produce these cells in a correct special and temporal tissue organization. Precedents for the successful construction of artificial genetic circuits have been reported. In general, these have been limited to simpler cells such as bacteria or yeast; however, we have ample preliminary results that demonstrate the successful construction of such circuits in mammalian cells. Thus, there is no insurmountable barrier to extending our results to stem cells. One of the laboratories (Weiss) in this proposal has pioneered the design and implementation of artificially controlled genetic circuits. The second laboratory (Lenischka) has been a leader in stem cell research for many years. Our joint expertise should facilitate the rapid progress of the studies in this proposal. We will begin by developing a number of "proof-of-principal" genetic circuits in mouse embryonic stem (ES) cells. We will take advantage of then known "master switch" molecules, and ask if we can build circuits where these "master switches" can be artificially controlled by small pharmaceutical agents used to treat the stem cells that have been genetically modified to contain the artificial circuits. We will address how effectively the stem cells can be triggered to produce alternate types of mature cells in response to controlled stimuli. These relatively simple circuits will also produce a wealth of necessary information regarding the dynamics and overall behavioral properties of artificial circuits in stem cells. Finally, we will take advantage of new results from the Lemischka laboratory that have begun to identify the naturally occurring regulatory components, pathways and networks that control biological functions of stem cells. We anticipate that the successful completion of the studies in this proposal will lay a broad and rigorous framework that will have broad applications in stem cell medicated repair of damaged tissues including the spinal cord.

Contact Information:
Ron Weiss, Ph.D.
Department of Electrical Engineering
Princeton University
B312 E-Quad Olden Street
Princeton, New Jersey 08540
609-258-3500

PRINCIPAL INVESTIGATOR – Martin L. Yarmush, M.D., Ph.D.
Grant Number 05B-023-SCR1
Basic Science Proposal
Grant Award $221,130

Project Title: Microfabrication of a Bioreactor System for Differentiation of Stem Cells into Neural Lineages

Incorporation of stem cell differentiation strategies into clinically relevant research endeavors, offers promising new approaches to therapeutic intervention. This is especially evident in the treatment of central nervous system injury and disease where mature neuronal cell implantation has met with both success and further challenges. In the case of spinal cord injury, the success of cell implantation protocols are limited by the non-permissive tissue environment, composed of both scar tissue and inhibitory molecules, secreted at the site of injury. In addition, the lack of readily available and renewable sources of mature nerve cells certainly limits the efficacy of cell implantation strategies. Clearly, the addition of stem cell research into this field offers the promise of readily available and renewable cell source. However, incorporation of stem cell research into spinal cord repair has two barriers to overcome. First, ethical issues have limited the potential of this endeavor. In addition, many differentiation protocols have been developed, which independently investigate the effect of a large number of variables on both the induction and maturation stages of neuronal differentiation. In essence, the tremendous effort extended in elucidating neural stem cell progenitor regulation by so many investigators and in so many different culture systems, has actually complicated extension of the basic research into clinical relevance. Therefore, developing an approach to systematically investigate the positive and negative variables, which regulate stem cell differentiation on a micro-scale, is critical in furthering the clinical adaptation of cell implantation following spinal cord injury. The additional benefit of this approach is that it reduces the number of stem cells needed for evaluation and testing of multiple parameters.

The proposed studies will develop a micro-scale differentiation environment. This microfabricated chamber will be used to optimize stem cell and adult neural cell culture approaches for the development of implantation protocols following spinal cord injury. This approach, using the most current microfabrication techniques, will be developed by an interdisciplinary team at Rutgers. The PI, Dr. Martin Yarmush, is a world-renowned tissue engineer and has a proven track record in design and development of microfluidically-controlled devices and in hepatic stem cell bioengineering. He now wishes to transfer these skills to area of spinal cord research. His expertise will be complimented by a team of co-investigators, skilled in neural and stem cell culture, and spinal cord injury models.

Contact Information:
Martin L. Yarmush, M.D., Ph.D.
Department of Biomedical Engineering
Rutgers, The State University of New Jersey
98 Brett Road
Piscataway, New Jersey 08854
732-445-4346

PRINCIPAL INVESTIGATOR – Wise Young, Ph.D., M.D.
Grant Number 05B-024-SCR1
Basic Science Proposal
Grant Award $391,704

Project Title: OEG Remyelination of Axons after Spinal Cord Injury

Olfactory ensheathing glia (OEG) cells normally reside in nasal mucosa, olfactory nerves and bulbs. These cells migrate alongside growing axons, secrete growth-promoting molecules, and may be why olfactory nerves regenerate in adult mammals. Several investigators have reported that OEG cells stimulate regeneration and remyelination when transplanted into cut spinal cords. However, when we transplanted OEG cells into rat spinal cords after contusion injury, which is more like most human spinal cord injuries, the cells did not survive or consistently improve functional recovery. Further studies showed that the environment of the acutely contused spinal cord is toxic to OEG cells and that the immune system rapidly rejected the cells. By transplanting OEG cells into the spinal cord surrounding the injury site, and suppressing the immune system with high-dose cyclosporin A (CyA), we showed that OEG cells not only survived for months, but migrated extensively into the injury site and surrounding cord and remyelinated many axons. Methylprednisolone (MP), a drug that is used to treat people with acute spinal cord injury, markedly enhanced survival of OEG transplants.

Dr. Hongyun Huang, a neurosurgeon who worked on some of these OEG experiments, went back to China and used a similar approach to transplant human fetal OEG cells into over 300 patients with spinal cord injury. The preliminary results of the trial revealed a surprising early recovery of motor and sensory function close to the injury site within several weeks, too rapid to be due to regeneration or remyelination. Although long-term data is not yet available from the trial, this early recovery is so striking that we propose a two-year study to investigate mechanisms of OEG-induced early recovery in rats, and to assess methods to enhance the beneficial effects of OEG transplants in spinal cord injury.

In the first year, we will determine whether OEG transplants stimulate sprouting and reconnection of axons close to the injury site in rats, whether OEG remyelination improves functional recovery, and whether CyA or MP affects regenerative sprouting after OEG transplants. In the second year, we will combine OEG transplants with a growth factor that may enhance the regenerative effects of OEG transplants: glial-derived neurotrophic factor (GDNF). We will assess the effects of using this combination therapy to enhance the regenerative effects of OEG transplants. These experiments are crucial for understanding what is happening after OEG transplants to the spinal cord, and to find ways to enhance the beneficial effects of this promising therapy for people with spinal cord injury.

Contact Information:
Wise Young, Ph.D., M.D.
W. M. Keck Center for Collaborative Neuroscience
Rutgers, The State University of New Jersey
604 Allison Road, D-251
Piscataway, New Jersey 08854
732-445-2061

FELLOWSHIP GRANT RECIPIENTS

PRINCIPAL INVESTIGATOR – Yu-Wen Chang
Graduate Fellowship
Grant Number 05B-001-SCR3
Grant Award $60,000

Project Title: Combination of Radial Glial Transplantation with Anti-Inflammatory Treatment in Rat Spinal Cord Injury

Cell transplantation is a promising strategy for spinal cord injury (SCI) research. Recent studies suggest that delayed implantation of embryonic stem cells or olfactory ensheathing cells promote axonal regeneration and improve behavioral performance. The rational for delayed transplantation is to prevent implanted cells from exposure to a non-favorable environment to yield a better survival rate. In our lab, we study radial glia and have been exploring their applications in spinal cord injury. Radial glial cells play essential roles in developing brain to guide and support neuronal migration. They are also neural stem cells that have the potential to become neurons and glia. Previous studies showed that radial glia migrated extensively in white matter in the normal spinal cord. We have acutely transplanted radial glia in the contused adult rat spinal cord and have demonstrated that radial glia cells have protective effect to the injured tissue and improve behavioral recovery. In this proposed study, we will conduct nine day delayed transplantation of radial glial RG3.6 to injured spinal cord.

Spinal cord injury triggers pronounced and progressive inflammatory and immune responses. A variety of inflammatory mediators are induced quickly in response to injury, which induces further cell death and tissue damage – so called secondary injury. Anti-inflammation is the current accepted acute phase treatment for human SCI. Several anti-inflammatory drugs used in rat models have been shown to be neuroprotective reducing lesion volumes and improving locomotor function. We will reduce secondary damage by anti-inflammatory drug immediately after the injury and conduct a nine day delayed radial glial transplantation in attempts to obtain a synergistic outcome. Our goal is to create a permissive environment by combining anti-inflammatory drugs with transplantation of cells to bridge the injury, promote injured axon regeneration and further enhance behavioral recovery.

Contact Information:
Yu-Wen Chang
W.M. Keck Center for Collaborative Neuroscience
Rutgers, The State University of New Jersey
604 Allison Road, Room D-251
Piscataway, New Jersey 08854
732-445-1781

PRINCIPAL INVESTIGATOR – Gary A. Monteiro
Graduate Fellowship
Grant Number 05B-003-SCR3
Grant Award $60,000

Project Title: Optimization of Stem Cell Differentiation with Microfluidics

The objective of this research is to quantify the mechanical and adhesive forces that govern stem cell differentiation into neurons. The derivation of in vitro differentiated stem cells into neuron cells has two-fold value. It helps us learn more about the early stages of neurogenesis as well as provide an unlimited source of neural transplantable donor cells for spinal cord disorders.

During embryonic development, there are mechanical, chemical and adhesive cues in the extra cellular matrix that direct stem cell growth. These signals change dynamically throughout development to orchestrate cell and tissue differentiation and organization. While much has been learned concerning stem cell fate, the interactions among cues are far from understood, especially in 3D environments, in which the cells reside in vivo. We believe in addition to chemical factors, mechanical forces as well as adhesion properties plays a role in the proliferation and differentiation of stem cells. Using microfluidics we propose to fabricate microenvironments of varying stiffness and adhesion properties to study the differentiation of stem cells into nerve cells in a combinatorial fashion.

Following completion of these aims, we will have defined a parameter space for the design of biomaterial scaffolds with optimum mechanical and adhesive properties for stem cell differentiation into nerve cells. Further, this research may be used as a basis to optimize the differentiation of stem cells into various other cell types.

Contact Information:
Gary A. Monteiro
Department of Biomedical Engineering
Rutgers, The State University of New Jersey
617 Bowser Road
Piscataway, New Jersey 08854-8014
732-445-8425

PRINCIPAL INVESTIGATOR – Christopher L. Gaughan
Graduate Fellowship
Grant Number 05B-004-SCR3
Grant Award $60,000

Project Title: Fabrication of a Tunable Hydrogel for Nerve Regeneration

The primary focus of my research is to design a hydrogel biomaterial that will provide the best combination of properties to entice spinal cord neurons to regenerate axons. In essence, this gel will serve as a pathway along which growing axons can migrate. In this proposal, I focus on optimizing the physical properties such that it maximizes this migration. It is known that neurons prefer softer, more porous materials, and inhibitory cells, such as astrocytes, prefer stiffer materials. Therefore, by modifying the physical properties, we can design a material that optimizes the likelihood of restoring neural connections. The gel is made up of four distinct protein subunits that link together and form an extensive hydrated network of fibers. By varying ratios of certain subunits used to form the gel, I hope to alter the stiffness of the fibers and thus optimize axonal migration. It is the modular nature of this design that enables such gel parameters to be controlled in this way. Furthermore, by using protein as the primary component of the gel, it is more amenable to bio-degradation. It could also be optimized for the purposes of injectability.

In this research proposal, I focus on the production of the subunits that will be used to make the gel described above. In short, four distinct protein subunits will be made using standard DNA cloning techniques. Four synthetic genes that code for each subunit will be cloned separately into small pieces of DNA that E.coli will propogate. E.coli can then serve as a type of factory wherein it can be made to produce the proteins that each of the genes encode for. Each protein produced in these E.coli has been specifically engineered such that it carries a tag that allows for its purification. After purifying each protein, I can mix them in the proper ratios that optimize the axonal growth characteristics of the gel. Furthermore, the DNA coding for two of the subunits can be modified to include ligands that specifically bind neurons and stimulate axonal growth cues, but are not permissive for astrocyte or fibroblast attachment.

The ultimate goal of this research is to fabricate a material that could be injected into a damaged or severed region of spinal cord. It is possible that once put in place; this gel could help “re-ligate” or join the ends of severed axons. In doing so, a significant step towards restoring the functionality of the cord would be taken.

A workable material such as I have described would have a significant impact on the citizens of New Jersey. Approximately 6,000 New Jersey residents suffer from traumatic injuries or diseases that damage the spinal cord. Estimates indicate that 300 new injuries occur each year in New Jersey. These injuries exact a considerable cost to the state and individuals, both monetary and emotional. Thus, any and all effective strategies that target spinal cord regeneration cannot be under-valued. I feel that my proposed biomaterial would be part of an effective strategy towards this end.

Contact Information:
Christopher L. Gaughan
Department of Chemical & Biochemical Engineering
Rutgers, The State University of New Jersey
98 Brett Road
Piscataway, New Jersey 08854-8058
732-445-5512