DIRECTORY OF GRANT AWARDS
2017 GRANT CYCLE

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

2017 GRANT CYCLE

DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

JUNE 2017

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 2017 grant cycle. The research projects are not categorized, or listed in any 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.nj.gov.

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:

CSCR17IRG010
KiBum Lee, Ph.D.
Rutgers, The State University
$600,000

Project Title: *A Biodegradable Nanoscaffold for the Co-Delivery of Patient Derived Neural Stem Cells and BET Inhibitor for Anti-Inflammation and Synaptic Restoration Post-SCI*

A novel biodegradable nanoscaffold loaded with BET inhibitors for improving stem cell and anti-inflammatory therapy simultaneously to effectively promote functional recovery after spinal cord injury. Spinal cord injury (SCI) is one of the most common causes of disability in young adults, affecting approximately 12,000 people in the United States every year. Spinal cord injury (SCI) results in many cellular dysfunctions that may cause severe and permanent neurological deficits. Several current therapeutic approaches are aimed at bridging the lesion site through cellular transplantation to restore neural signaling, reduce inflammation, and prevent subsequent damage to the injured area. Given the intrinsically limited regenerative potential of the central nervous system (CNS) and the complex inhibitory environment of the injured spinal cord, effective strategies to generate a robust population of functional neurons derived from autologous neural stem cells (NSCs) re-establishing the damaged neural circuitry are urgent clinical needs. However, several pertinent obstacles hinder successful transplantation strategies. First, due to the inflammatory nature of the injured spinal cord, most NSCs die soon after transplantation. Second, the extracellular matrix of the injured spinal cord is not very conducive to NSC survival and differentiation. Thus, we will address these challenges by combining a novel bioscaffold with a small compound that reduces inflammation and promotes neuronal differentiation.

To address the aforementioned challenges in SCI, the overall objectives of this proposal are: i) to develop a multifunctional nanomaterial-based bioscaffold methodology for the controlled delivery of therapeutic molecules; ii) to incorporate nanomaterial-based bioscaffold into the enhanced transplantation of human-induced pluripotent stem cell (iPSC)-derived neurons; and iii) to evaluate the combined therapeutic effect of spatiotemporal delivery of therapeutic molecules and stem cell therapy for the effective treatment of SCI using a rodent SCI model. Our proposed biomaterial scaffolds that mimic the properties of the natural microenvironment can be promising candidates for stem cell-based tissue engineering. Considering the difficulties of generating a robust population of functional neurons and enhancing neuronal behaviors (neurite outgrowth and axon regeneration), our biodegradable hybrid nano-scaffold can serve as a powerful tool for achieving an improved SCI treatment.

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NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

CSCR17IRG007
Stella Elkabes, Ph.D.
Rutgers University BHS
$600,000

Project Title: *The Astroglial Response to SCI: Modulation by a TLR9 Antagonist*

The effects of a TLR9 inhibitor on astrocyte function at the glial scar are investigated in mice sustaining a SC contusion injury and the underlying mechanisms are delineated in astrocyte cultures. Spinal cord trauma causes extensive tissue and cell loss at the affected site, disrupts the axons of nerve cells that mediate the communication between the brain and other parts of the body, and leads to permanent deficits including paralysis. Many molecular and cellular perturbations occur at the injury site, which worsen the damage caused by the initial trauma. A cell type found in the spinal cord, called astrocyte, responds to injury by altering its function. Astrocytes are the most abundant cells of the central nervous system and play many essential roles in both health and disease. Following injury, astrocytes divide, accumulate around the lesion and become an essential component of a scar that separates the healthy tissue from the wounded region in order to contain the damage and prevent further harm. However, this scar also constitutes a barrier to the repair of injured axons, partly because astrocytes release molecules that inhibit axonal growth. In addition, astrocytes promote the expansion of the inflammatory reaction at the injury site by secreting factors that attract inflammatory cells. Paradoxically, astrocytes protect nerve cells from death and support the viability of cells spared by the initial trauma. Given the multitude of important roles played by astrocytes following spinal cord injury (SCI), it is critical to understand how they change their function in response to trauma and to discover new approaches that enhance their beneficial effects while reducing their deleterious influences.

Encouraging preliminary investigations have shown that astrocyte function can be altered by a pharmacological inhibitor of toll like receptor 9 (TLR9). Toll like receptors (TLRs) are important components of the immune system but are also found in cells of the spinal cord and the brain. They mediate the response of the body to infection and to injury or diseases that occur in the absence of infectious agents. TLRs play various roles following SCI, including regulation of the inflammatory reaction at the affected site. In accordance with this idea, earlier studies in this laboratory have shown that a TLR9 inhibitor reduces the number of inflammatory immune cells that infiltrate the injury epicenter and limits the development of chronic pain and bladder dysfunction associated with SCI. Even though TLR9 is found in astrocytes, it is not yet known how it influences astrocyte function at the scar.

The studies proposed in the present application will investigate how treatment with the TLR9 inhibitor changes the beneficial and detrimental functions of astrocytes at the scar, in mice sustaining a severe spinal cord contusion injury. In addition, studies will be performed to elucidate the underlying mechanisms by utilizing models that mimic injury in spinal cord astrocytes grown in dishes. The alteration of astrocyte function by the TLR9 inhibitor, could

modify the properties of the scar, leading to improved axonal repair and protection of nerve cells. The discovery of new agents that can simultaneously enhance the restorative effects of astrocytes while attenuating the actions that hamper recovery could alleviate the devastating outcomes of SCI.

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EXPLORATORY RESEARCH GRANT RECIPIENTS:

CSCR17ERG007
Eunsung Junn, Ph.D.
Rutgers University BHS
$200,000

Project Title: *Effect of microRNA-7 in Spinal Cord Injury*

We plan to investigate the potential therapeutic effect of microRNA-7 in a mouse model of spinal cord injury. A spinal cord injury is the damage to the spinal cord, which causes permanent changes in strength, sensation and other body functions below the site of the injury. In the United States, the occurrence of spinal cord injury has been estimated to be about 40 cases per 1 million people per year or around 12,000 cases per year. Currently, there are no effective therapies for the treatment of spinal cord injury. The first mechanical damage initiates a complex set of secondary molecular events that largely determine the symptoms of the spinal cord injury (SCI). Diverse cellular mechanisms responsible for this secondary injury mostly depend on changes of specific gene programs.

Since the first discovery in worm in 1993, microRNA (miR)-dependent gene regulation has been widely studied in a variety of eukaryotic organisms. MiRs are a class of 20-25 base-long RNAs that negatively regulate gene expression by binding to their target RNA sequence. Accumulating evidence suggest its key role in the pathogenesis of various diseases. Our published and preliminary data showed that microRNA-7 (miR-7) exhibits a protective role in the cellular models of oxidative stress. In particular, miR-7 accomplishes neuroprotection by improving the health of mitochondria, a powerhouse in the cells. Mitochondrial activity is severely compromised following spinal cord injury, thus improving mitochondrial health could have therapeutic value for the treatment of spinal cord injury. In the current application, we propose to investigate whether miR-7 promotes the functional recovery from spinal cord injury using a mouse model. MiR-7 will be delivered to injury sites using viral vector and gold nanoparticle, and its effect on locomotor behavior and cellular response will be assessed at 6 weeks post-delivery. We expect that miR-7 presents better motor functional recovery from the severe spinal cord compression, and that miR-7 can be developed as a potential therapeutic for spinal cord injury.

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CSCR17ERG005
Bonnie Firestein, Ph.D.
Rutgers University
$200,000

Project Title: *Targeting Cypin for Neural Circuit and Motor Function Recovery Following SCI*

We will use drugs that target the protein cypin to promote nerve cell signaling and motor function after SCI. Spinal cord injury (SCI) causes widespread neuronal damage and dysfunction, often leading to severe motor deficits, which impair lives of affected individuals. The process of neuronal damage following SCI involves rapid release of glutamate from injured neurons, which causes further damage. Our group and others have shown that uric acid, a compound that naturally occurs in the body, promotes survival of neurons after they are injured. We have identified a handful of drugs that activate enzymes in the brain that produce uric acid. We have shown that these compounds help other types of neurons function after injury when the neurons are treated in a culture system.

We now propose to move our studies into the intact animal using a spinal cord contusion injury model. The value of such a study would be considerable, as it could provide information that could ultimately be used to influence neuronal survival after spinal cord insult in a way that could enhance motor function and the outcome of rehabilitative training after spinal cord injury. Thus, our hope is to develop novel therapies to cure paralysis after spinal cord injury

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CSCR17ERG006
Martin Yarmush, Ph.D.
Rutgers University
$200,000

Project Title: *Pulsed Electric Fields for Spinal Cord Injury Wound Treatment*

The current studies will investigate the efficacy of pulsed electric fields as a multi-modal SCI treatment for pressure wound healing and infection control.

Pressure ulcer treatment has emerged as a particularly confounding medical problem, with an annual cost of over $11 billion per year in the US. Spinal cord injury patients are particularly susceptible to pressure wound development with an incidence of over 50% and there are approximately 400 new patients per year who suffer from spinal cord injury in New Jersey. Among the factors that specifically increase spinal cord injured patient risk is loss of sensation and mobility, resulting in unrelieved pressure on tissues over bony structures, reduced micro-circulation and ultimately tissue necrosis. A second but major consequence of pressure ulcers is bacterial colonization within the wound which can result in sepsis and patient death. The fact that normal wound healing is compromised in spinal cord injured patients, further complicates patient treatment and increases risk of infection. However, with the emergence of antibiotic resistance strains, antibiotic treatment may be problematic especially in patients who suffer from repeated pressure wound and infection cycles. Therefore, finding an effective pressure wound treatment for spinal cord injury patients will help to resolve a very large problem associated with both patient mortality and growing financial costs. We believe that pulsed electric fields can be used as a multi-modal treatment for spinal cord injury patients to 1) improve pressure wound closure and 2) prevent bacterial overgrowth in the wounds thereby reducing patient morbidity and mortality. Given our recent success in applying this technology to burn wound injury treatment, the proposed studies will determine whether this approach can also be used to treat pressure wounds and their infections following spinal cord injury. However, since spinal cord injury also compromises normal wound healing, the challenge of this exploratory proposal will be to test and/or optimize our technology for pressure wound and bacterial control following spinal cord injury in a mouse model. The development of a chemical-free, relatively low cost, multi-targeted therapy for SCI pressure wound healing and disinfection will be a major and significant step forward in this field.

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CSCR17ERG010
David I. Shreiber, Ph.D.
Rutgers University
$200,000

Project Title: *Multi-Scale Modeling of Dynamic Behavior of White Matter*

We will characterize how individual axons respond to dynamic loading in situ, and use this information to significantly expand and enhance a multi-scale computational model of white matter mechanics. Spinal Cord Injury (SCI) begins with mechanical trauma that deforms and damages tissue. This mechanical injury leads to a series of secondary injuries, which begin to develop minutes after injury and can continue to damage cells for weeks. Although these secondary injuries are the main target for clinical therapies, the devastating consequences of SCI are best avoided by preventing the primary injury. To rationally design means and develop measures to avert these injuries, to understand the severity and extent of primary SCI and relate it to secondary injury, and to develop reproducible and relevant in vivo and in vitro models of SCI, a thorough and complete understanding of the mechanics of the tissue is required. The mechanics are complicated because spinal cord tissue is not a "solid" in the traditional sense. It is composed of cells and other microscopic entities that combined give it properties at a much larger scale. However, it is these microscopic entities that are damaged and are responsible for the loss of physiological functions. In particular, damage to axons in the white matter of the spinal cord is the largest contributor to physiological and functional deficits following SCI. An axon is the part of the neuron that connects it to the next neuron or the end target, such as a muscle. Thus, when axons are damaged, signals from the brain to the periphery and from the periphery back to the brain cannot be propagated.

White matter is primarily composed of bundles of these axons and cells that wrap a fatty substance called myelin around the axons. The myelin acts as an insulator to improve the speed of electrical signals similar to insulation around a wire. We have shown that these myelinating cells, which are called oligodendroyctes, also mechanically couple axons together and change the mechanical behavior of the tissue. We have also developed an approach to study the multi-scale mechanics of white matter in situ – that is, how the individual axons in their natural state stretch when the whole tissue is stretched, and how this relationship is influenced by oligodendrocytes – and we have incorporated the information into a computer model of this multi-scale behavior.

However, our previous characterizations and models have some significant limitations that we aim to address in this proposal. First, and most importantly, we developed the model from data collected after stretching spinal cord samples very slowly. However, trauma in SCI occurs very quickly – on the order of a few milliseconds – and we know that the mechanical response of the axons is different when they are stretched quickly and slowly. We will develop an innovative approach using flash-freezing to capture the changes in axons that occur when stretched very quickly. Second, we previously identified strain thresholds above which an axon would break based on complete mechanical failure of axons, but we know that an axon will functionally fail before it completely physically fails. We will characterize disruptions in the axonal cytoskeleton following dynamics stretch. Finally, we have determined strain thresholds for axons, but some evidence suggests that axons may be more sensitive to mechanical stress than strain. To study stress at the axon level, we will determine the mechanical properties of individual axons in situ

when myelinated and not myelinated. Then we will incorporate these properties and the dynamic characterizations into our computer model of white matter mechanics. This model will allow us to study how stress and strain are distributed among axons when the tissue experiences dynamic mechanical loads, and how the stress and strain are redistributed once axons begin to fail. This model can then be used to identify the circumstances that cause SCI, to assess the extent and severity of primary axon injury in these circumstances, and to rationally design and develop approaches to prevent these circumstances.

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SPINAL CORD TECHNIQUES TRAINING TRAVEL GRANT RECIPIENTS:

CSCR17TTT007
Mohammed Abdul Muneer Peringady
JFK Medical Center
$4,000

My laboratory focuses on understanding the underlying mechanisms of central nervous system (CNS) injury emphasizing spinal cord injury (SCI) mediated neurological dysfunctions with the objective of developing effective therapeutic strategies. Our primary focus is on unraveling the inter/intracellular signaling pathways and role of various regulatory factors involves in neuronal/axonal regeneration in the CNS after injuries. We use in vivo model of hemisection SCI and in vitro stretch injury model to elucidate the mechanisms of injury to locate target mechanism to develop therapeutic strategies against CNS injury. In addition, we employ various other in vitro and in vivo research approaches, including blocking of repulsive signaling pathways using pharmacological methods, virus vector-mediated gene transfer to the SCI site and brain, survival animal surgeries etc. Now I am looking forward the opportunities to expand my research sphere by incorporating more relevant techniques and models of CNS injuries.

Currently, we are focusing on effective therapeutic interventions targeting the major mechanisms of axonal regeneration for developing clinical methods for SCI patients. There are several intrinsic factors including phosphatase and tensin homolog (PTEN), phosphatidylinositol 3-kinase (PI3K), suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase (PTP) that controls axonal regeneration by controlling gene expression after CNS injury. It is well established that PTEN, a negative regulator of mammalian target of rapamycin (mTOR), appears to be particularly important for controlling the regenerative capacity of injured axons after CNS injury. Conditional deletion of PTEN remarkably enhances axon growth after SCI or optic nerve injury (ONI). Recently, we reported that PTEN antagonists peptides enhances axonal regeneration and promotes functional recovery after SCI in mice. PTEN inhibition potentiates axonal sprouting in ONI and SCI through induction of PI3K/Akt sign¬aling and activation of mTOR. Similar to PTEN, suppressor of cytokine signaling 3 (SOCS3, a negative regulator of Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway) has a significant role in regulating axonal regeneration after CNS injury. In another pathway, the chondroitin sulfate proteoglycans (CSPGs) inhibit neuronal growth by binding and activating two PTP receptors, PTPσ and LAR. Intracellularly, activation of PTPσ and LAR by CSPGs activate RhoA-Rock signaling and inactivate Akt and Erk pathways.

Recent investigations have revealed the prospects of growth promoting/differentiating signaling proteins as therapeutic agents against SCI conditions. We will enhance the level of these growth-promoting/differentiating factors by introducing the gene via lentivirus vector tailored with a highly efficient promoter and green fluorescent protein (GFP) into sensori-motor cortex of brain and to the sites of hemisection SCI (rostral to the lesion) of injured mice and evaluate their role in promoting axonal regeneration. Therapeutic approaches using gene therapy have been reported in various animal models of different CNS injuries including traumatic brain injury (TBI), SCI and ONI. In vivo gene delivery to the sites of SCI has been useful in identifying

patterns of axonal sensitivity to growth factors both in acute and chronic SCI. It also directs long-term transgene expression in neurons and glial cells and this allows us to perform long-term functional recovery studies to investigate the efficacy of cell and gene-based repair strategies.

From the Spinal Cord Injury Techniques Training Grant, I am anticipating an extensive exposure to various techniques and methods in SCI in the form of features lectures, demonstrations, and hands-on experience in all facets of spinal cord injury research, as well as training in surgery, animal care, behavioral studies, and outcome measures. This training will help me to closely interact with the pioneers in SCI and improve my understanding of spinal cord injury and strengthen my research. In addition, this training will allow me to apply my gene therapy expertise to spinal cord research more effectively, so that I can conduct innovative and effective research to develop therapeutic strategies against spinal cord injury.

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CSCR17TTT008
Kathlyn Laval, Ph.D.
Princeton University
$4,000

The aim of the applicant NJCSCR fellowship project is to set up a new animal model of neuropathic itch. By characterizing the cellular and molecular mechanisms of neuropathic pruritus induced in mice by pseudorabies (PRV), an alphaherpesvirus, the applicant will determine whether virus-induced inflammation and damage of peripheral nervous system (PNS) neurons and spinal cord contribute to the development of neuropathic itch symptoms. This research will provide a better understanding of how viral-induced damage to the PNS and spinal cord produces neuropathic itch in mammals.

In this context, attending the spinal cord injury course will be a unique opportunity for the applicant to learn new techniques which have the potential to widen the scope and practical applicability of her research project considerably. Such a course will also allow the applicant to interact with experts in the field, foster collaborations, and will also be a source of new ideas and approaches. The scientific and leadership training founded by this application will provide a solid foundation to increase the likelihood of successful appointment of the applicant to a tenure-track academic faculty position working on the pathogenesis of neurotropic viruses with a particular interest in clinical applications of these findings in SCI research.

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NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

CSCR17TTT009
Sinan Gok, Ph.D.
New Jersey Institute of Technology
$4,000

I am applying for the NJCSCR's Spinal Cord Injury techniques training travel grant. I am a PhD candidate in the Department of Biomedical Engineering at New Jersey Institute of Technology. I have been working on the "Chronic recordings from the descending pathways of rat spinal cord" project for about five years now. I am currently investigating the correlations between the forelimb muscle activities and descending neural signals in behaving rats. My initial findings, which were presented in various conferences, show that forelimb EMG signals can be accurately predicted using the neural data that was recorded during a reach-to-pull task. I have been using a custom made ECoG-type electrode array to record this data. However, there is still plenty of room for improvement in terms of insertion techniques, signal quality and selectivity. In order to address many challenges that I have faced with the current electrode, I am proposing to use a new recording electrode, namely, carbon fiber multi-electrodes (CFMEs). CFMEs are made of very small caliber carbon fiber filaments (5-7 µm) with small footprints which make them attractive for neural recordings. However, the implantation procedure will be very challenging. Learning new surgical techniques and sharing hands-on experiences with other colleagues will surely help me to improve the success of my experiments.

I have been trained by Dr. Mesut Sahin, one of the experts in rat spinal cord surgery for chronic electrode implants. Innovative techniques that were developed by Dr. Sahin allowed us to collect long-term data from freely moving rats. As his assistant in surgeries, I took part in preparing the animals for surgery, monitoring the vitals during operation, and making incisions for electrode implants. I have gained skills on epimysial EMG wire placement and dorsal laminectomy. I have also had experience with brain craniotomy for neural stimulation. I believe that my field of study is strongly correlated with the Ohio State University's SCI Research Training Program. The objectives of the program including to teach proficiency in spinal cord laminectomy, post-operative care, behavioral assessment of locomotor function, to provide hands-on experience with rodent injury models and surgical approaches can greatly help me to improve my experimental skills.

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