DIRECTORY OF GRANT AWARDS
2012 GRANT CYCLE

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

2012 GRANT CYCLE

DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

JUNE 2012

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 2012 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.

2012 MEMBERSHIP INFORMATION

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NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

Joachim Kohn, Ph.D. Grant Award: $593,018
New Jersey Center for Biomaterials
Rutgers, The State University of New Jersey

Project Title: *Improved Implantable Micro-Electrodes for Neural Signal Acquisition*

To enable long-term performance of brain computer interfaces for controlling neural prosthetic devices, this project will develop long-term implantable microelectrodes, or probes. Though once believed to be purely science fiction, bypassing the impaired neuromuscular system to control external devices with thoughts alone is increasingly seen as a viable option for patients who have suffered a spinal cord injury (SCI). Using a device known as a "brain-computer interface" (BCI), signals from the brain are acquired, decoded, and translated into machine commands to perform specific tasks intended by the patient. The signals can be used to (i) bypass the spinal cord and relay information directly to the body, or (ii) to control a device, such as a wheelchair or computer. BCI systems have been shown to re-establish some level of independence and thus, contribute significantly to the quality of life for people with devastating neurologic injuries such as SCI.

While there are other critical components to a functional BCI, the most essential element is getting a strong lasting signal from the brain. Although surface recordings have been somewhat successful, they are not as potentially useful as signals taken from deeper within the brain. Several groups have demonstrated the feasibility of recording nerve signals using implanted microelectrodes, also called probes. Unfortunately there are issues when the current generation probes are implanted in the brain. A process of tissue scarring, called gliosis occurs rendering the probes ineffective within a few months. Various approaches focusing on probe material and design have been investigated to limit the reactions and improve long-term performance. There are two principal theories: (i) larger implanted devices cause damage, and lead to long-lasting gliosis because of a size mismatch compared to cells, and/or (ii) devices made of materials that are less flexible than the surrounding brain tissue induce gliosis. For both, implant size is the key variable, leading to the theory that large, rigid implants are recognized as a foreign body, and small implants are not. Thus, smaller, more flexible devices may reduce gliosis and improve long-term device performance. In this project, we propose to develop small, flexible probes with a strong non-toxic, biodegradable, absorbable polymer coating that will reduce chronic gliosis. Neural recording from probes implanted for the long-term holds great promise for development of rehabilitation strategies following SCI, but the effectiveness of the microelectrodes is limited by gliosis around the probe. We believe that small, flexible probes will reduce or eliminate gliosis. However, they will lack the structural stiffness to be implanted. To solve this problem, we will coat the probes with a rapidly degrading polymer that temporarily increases the probe stiffness to allow insertion, and then degrades to expose the probe. In this project, we will optimize the design of the probe and polymer coating.

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Melitta Schachner, Ph.D.
Department of Cell Biology & Neuroscience
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Grant Award: $357,905

Project Title: *Therapeutic Potential of miRNA 133b in Spinal Cord Injury*

We will investigate functional recovery after spinal cord injury in mouse by application of a microRNA that enhances regeneration in zebrafish and may promote functional recovery in mammals. We have discovered a microRNA (microRNA 133b) that enhances regeneration after spinal cord injury in adult zebrafish, which have the potential, in contrast to mammals, to recover functionally and structurally from complete transection of the spinal cord. This microRNA, which is conserved in sequence across many animal species, including fish, mouse and man, will be tested in the non-regenerating mouse model of spinal cord injury by application of a stable synthetic microRNA and a non-replicative virus (adeno-associated virus which is used in over 50 clinical trials worldwide).

The effects of microRNA 133b on regeneration from spinal cord injury will be tested in acutely injured mice by several criteria for regeneration: walking function, nerve regeneration, sparing of white matter, and suppression of glial scar formation as well as other molecules that inhibit regeneration. We will also test its capacity to modulate the immune response, as treatments that reduce acute inflammation have shown to positively affect functional recovery after injury. In parallel, we will monitor the effects of microRNA 133b application on pain and sensitivity to touch.

These studies are designed to form the basis for validation of the beneficial properties of microRNA 133b in a mammal with very limited capacity for functional and structural recovery from spinal cord injury in adulthood. The aim is to develop microRNA 133b into a reagent that can be applied for therapy in humans.

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Martin Grumet, Ph.D.
Department of Cell Biology & Neuroscience
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Grant Award: $499,207

Project Title: *Molecular & Functional Analysis of Minimally Invasive Lumbar Delivery of Encapsulated MSC for SCI*

Our goal is to analyze the protective effects of mesenchymal stem cells (MSC) in injured spinal cords so that we can maximize the beneficial effects of injecting MSC after injury using a rat model. The use of mesenchymal stem cells (MSC) for clinically relevant treatments of spinal cord injury (SCI) is supported by data indicating that MSC modulate inflammatory reactions, reduces loss of cells, and improves functional outcomes after neural trauma. We have found that both freely migrating and encapsulated MSC in culture and after injection into the injured spinal cord are anti-inflammatory. A main objective of this study is to analyze the beneficial effects of encapsulated MSC on inflammatory cells such as macrophages. We will focus on the encapsulated MSCs because they were more effective in enhancing anti-inflammatory factors and reducing pro-inflammatory factors than freely migrating MSC both in culture and in SCI. moreover, the encapsulation protected MSC survival in the injured spinal cord. Our goals are to analyze MSC effects on specific types of inflammatory cells and factors in culture and during recovery of function in rat SCI.

Toward these goals, we will pursue two aims: 1. To analyze effects of MSC on activated macrophages that are recruited to the spinal cord after injury and on microglia, the resident immune cells of the spinal cord. Studies will first be done in culture with isolated cells to identify changes in specific inflammatory factors, which will then be analyzed in SCI after MSC injection. To measure biochemical effects of encapsulated MSC in rat SCI, MSC will be injected intrathecally into the lumbar enlargement (a procedure similar to the "epidural" commonly used during human delivery) and spinal cord tissue will be tested for changes in inflammatory factors distribution. Changes in the inflammatory factors will serve as criteria in additional experiments to optimize the number and density of MSC in capsules that yield maximal increases in anti-inflammatory and decreases in pro-inflammatory factors. Capsules in the spinal cord will be examined to determine MSC viability over time. 2. To analyze functional effects of encapsulated MSC in SCI, rats will be allowed to survive for 8 weeks while measurements of locomotion and pain will indicate the degree of recovery. After sacrifice at 8 weeks, effects of MSCs on immune and neural cells in the spinal cord surrounding the injury will be analyzed histologically to measure the persistence of inflammation and neuroprotection. Biochemical changes in mRNA and protein expression in and around the injury site will be analyzed in tissue extracts from other rats with similar treatments. The results of these studies will determine whether the optimized MSC capsule yield better outcomes in rat behavior and expression of inflammatory factors after SCI. To determine how further delays in MSC treatment compromises their effects, we will compare 8-week effects of our standard delay of 1 day with delays of 2 and 7 days. The combined results will optimize efficacy of MSC capsules in SCI, provide a window of opportunity for treatment and perhaps biomarkers for the MSC effects that will provide a platform for evaluating this clinically-relevant method of delivering encapsulated cells by lumbar puncture.

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Stella Elkabes, Ph.D.
UMDNJ – New Jersey Medical School

Grant Award: $598,449

Project Title: *Effects of TLR9 Ligands on the Inflammatory Response, Bladder Dysfunction and Chronic Pain in Spinal Cord Injury*

Damage to the spinal cord frequently results from an initial mechanical trauma that causes tissue destruction, cell death and disruption of nerve fibers that connect the brain with the spinal cord. This is followed by changes in the spinal cord including inflammation, which worsens the outcome of the injury. The inflammatory cells produce substances that further harm the remaining cells and nerve fibers, while preventing regeneration. However, not all inflammation is bad. Some inflammatory cells produce substances that enhance tissue repair. Therefore, the balance between the beneficial and detrimental effects of inflammation could impact the outcome of spinal cord injury (sci). Little is known about treatments that alter the inflammatory reaction such that the proportion of cells that produce helpful substances is increased and those that produce harmful substances are decreased. The overall goal of the studies is to evaluate a new treatment that potentially reduces the harmful actions of inflammation while enhancing the protective effects and improves impaired bladder function and chronic pain, two common secondary complications of sci. Inflammatory cells that invade the injured area of the spinal cord express toll-like receptors (TLR) which are best known for activating the immune system in order to protect the host against bacteria. However, TLRs are also present in the central nervous system and have been implicated in the inflammation that follows trauma, albeit their exact contribution is poorly understood. It is believed that damaged cells release mediators that activate TLRs and thereby, modulate the inflammatory response. Preliminary investigations in this laboratory indicated that the delivery of a synthetic TLR9 activator to the spinal fluid amplifies the inflammatory reaction and worsens urinary bladder function in mice sustaining a sci. In contrast, a synthetic blocker of TLR9 attenuates inflammation and improves bladder function. It is well known that inflammation can intensify chronic pain experienced after sci. Based on these findings, it is proposed that a TLR9 activator aggravates the detrimental effects of inflammation and exacerbates bladder dysfunction and chronic pain. In contrast, an antagonist can be used as a therapy to enhance the beneficial properties of inflammation, improve bladder dysfunction and reduce chronic pain.

The studies described in this application use mice with sci. The TLR9 activator and blocker are delivered into the spinal fluid by lumbar puncture and the proportion of different types of inflammatory cells are evaluated at various times following treatment in order to determine the changes observed. In addition, the effects of the treatment on recovery from paralysis, bladder control and hypersensitivity to heat are assessed. The molecular mechanisms underlying some of the effects of the TLR9 activator and blocker are also explored. It is anticipated that the proposed investigations will shed light not only on TLR9 function in sci but also determine whether the TLR9 blocker can be used to modulate inflammation, improve bladder function and lessen chronic pain. The long-term goal of these studies is to provide a pre-clinical foundation that can support future investigations on the therapeutic potential of the TLR9 blocker in individuals with sci. Some TLR9 activators and blockers have already been approved in clinical trials of other pathological conditions and as such, this could facilitate the design and use of additional activators and blockers to treat complications associated with sci.

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NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

GRANT AWARDS

FELLOWSHIP GRANT RECIPIENTS:

Ying Li Grant Award: $60,000
Department of Biomedical Engineering
Rutgers, The State University of New Jersey

Project Title: *Molecular Mechanism of Notch1 Expression in Spinal Cord Development and Post-SCI Response*

This project is to study the functional role of a Notch1 enhancer and its trans-acting protein factors in spinal cord development in order to provide novel knowledge for spinal cord injury therapy. An unfortunate aspect about spinal cord injury (SCI) is that the damage cannot be reversed, but new treatments are under investigation in labs like my mentor's to find experimental methods that can terminate cell death and promote neural regeneration. The long-term objective of this project is to elucidate the molecular mechanisms that govern gene expression, cell differentiation and axon myelination during spinal cord development, cell death and regeneration after SCI. Understanding of such mechanisms is the basis of cell-based therapies for SCI. The proposed project will focus on the regulation of Notch1 expression. Notch1 is a member of the transmembrane protein family encodes a single-pass transmembrane receptor. It plays a critical role in the development of the central nervous system (CNS) by inhibiting neuronal differentiation, maintaining neural progenitor character, promoting glial differentiation, specifying glial cell type and promoting apoptotic cell death. Notch1 inactivation in the spinal cord results in an accelerated neural differentiation in ventral spinal cord and gradual disappearance of the ventral central canal. Moreover, all subtypes of neural progenitor cells decrease in number, while V0-2 interneurons increase at the expense of some motoneuron subtypes. Although the functional roles of Notch1 in the development of spinal cord have been established, the molecular mechanism that governs the expression of Notch1 is still poorly understood.

Recently, a novel cis-regulatory element of Notch1 (Notch1CR2) that directs gene expression exclusively in the CNS was identified in my mentor's lab using computational and molecular genetics methods. Preliminary study on Notch1CR2 shows its ability to drive reporter gene expression during early embryonic neurogenesis in chick and mouse. Evidences of Its activity in neural stem cells (NSC) suggest its involvement in the regulation of neural cell fate determination. It is highly possible that Notch1CR2 can also regulate NSC re-activation post SCI. Thus here, I propose to investigate the roles of this cis-element and its interacting trans-acting factors in regulating Notch1 expression during normal spinal cord development and after SCI. Full accomplishment of this project will provide possible investigating targets for further spinal cord injury research in both pathological and therapeutic fields.

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Nathan Schroeder Grant Award: $150,000
Human Genetics Institute
Rutgers, The State University of New Jersey

Project Title: *Stress-Induced Neuroplasticity in C. elegans: A New Paradigm to Study Neuronal Outgrowth Following Spinal Cord Injury*

Stress-induced neuroplasticity in C. elegans: A new paradigm to study neuronal outgrowth following spinal cord injury. Spinal cord injuries (SCI) affect over 1 million Americans. Many of the secondary effects resulting from SCI (cardiovascular disease, post-SCI pain, bladder dysfunction) are correlated with the growth or new formation of processes from surviving neurons (i.e. neuroplasticity). Plasticity in surviving neurons is also associated with spontaneous recovery from SCI. While neurobiologists have made great strides in understanding normal development of neuronal processes, it is unclear how plasticity occurs following a traumatic event such as SCI. One factor potentially underlying this plasticity is stress. Researchers have shown that stress-related hormones are increased following SCI and that these same stress-related hormones play an important role in neuroplasticity. A better understanding of how stress affects neuroplasticity may lead to novel treatments for SCI rehabilitation and treatment for SCI-related dysfunctions.

The roundworm Caenorhabditis elegans is a well-studied model organism. Similar to mice and fruit flies, C. elegans has been used to understand numerous human neurological disorders and to study fundamental questions in neuroscience. C. elegans has a simple nervous system, a very short life-cycle allowing for rapid experimentation, a transparent skin allowing for visualization of neurons in live animals, and a completely sequenced genome allowing for comparison to the human genome. I recently discovered that under conditions of stress, a specific class of C. elegans neurons undergoes neuroplasticity. For example, specific neuronal processes undergo a 300% increase in length, while other brand new processes are born. Following a return to non-stressful conditions, these processes resorb and return to their previous non-stressed morphology. Given the ease of experimentation in C. elegans, we propose using our new discovery to understand the mechanisms of stress-induced neuroplasticity.

In addition to an in-depth characterization of this phenomenon, I have already identified several genes that regulate this stress-induced plasticity. For this fellowship I will continue to identify new genes that affect this stress-induced plasticity. I will also characterize the mechanism by which these genes act. Finally, I will use advanced microscopy techniques to uncover the changes that occur within the neurons during this plasticity. The results of this fellowship may lead to new insights into neuroplasticity following SCI.

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NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

GRANT AWARDS

SPINAL CORD TECHNIQUES TRAINING GRANT RECIPIENTS:

Cheul H. Cho, Ph.D. Grant Award: $2,500
New Jersey Institute of Technology

Stem cell-based therapies for the repair of spinal cord injury have become increasingly popular due to their ability to not only replace lost cell types, but also aid in regeneration. I have over 12 years of research experience in the field of stem cells. I have developed a novel differentiation technique of pluripotent stem cells into endoderm lineage and filed a full patent application in 2010. Ongoing projects in my laboratory include: 1) regulation of oligodendrocyte differentiation from pluripotent stem cells for the repair of spinal cord injury and 2) development of functional 3-D tissue models for tissue repair and regeneration. The Spinal Cord Injury Techniques Training Grant will allow me to apply my stem cell expertise to spinal cord research. This training grant will also provide me with valuable knowledge and hands-on experience in spinal cord research, so that I can conduct innovative and effective research for the repair of spinal cord injury.

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Mazell Tetruashvily, M.S. Grant Award: $857
Princeton University

My goal in enrolling in the spinal cord injury course hosted by Rutgers University W. M. Keck Center for Collaborative Neuroscience is to further my knowledge in spinal cord injury and enhance my research in a manner that would yield promising new advances in the field. My current laboratory research explores the core mechanisms of peripheral synapse loss, a primary deterrent to neuronal regeneration following spinal cord injury, by testing the hypothesis that members of the major histocompatibility complex class I (MHCI) are required for synapse elimination at the developing NMJ. This course, featuring lectures, demonstrations, and hands-on experience in all facets of spinal cord injury research, as well as training in anesthesia, locomotor scoring (BBB), animal care, and outcome measures, will aid in my understanding of spinal cord injury and consequently strengthen my research.

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