NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

2005 A CYCLE

DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

JUNE 2005

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 2005 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 PO 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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NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

PRINCIPAL INVESTIGATOR – **Yasuhiro Maeda, M.D**.
Basic Science Proposal
Grant Award – $393,800

Proposal Title: Effect of Erythropoietin Therapy on Acute Traumatic Spinal Cord Injury and Mechanism of Action

We plan to study the effect of erythropoietin (Epo) on traumatic spinal cord injury. We believe Epo may be an effective form of therapy that mediates its effect through downmodulating immune reactions within the injury site in the spinal cord. To test this possibility, we will first measure the effect of therapeutic intervention with erythropoietin on wild type mice using untreated spinal cord injured wild type mice as a control. As a second measure of therapeutic effectiveness, we will measure the histopathologic alterations at the site of injury in treated and untreated control cord injured animals. We predict that erythropoietin will limit the area of pathology to much smaller dimensions. The findings from these first experiments will then be compared to a second series of experiments in which immunodeficient RAG1 -/- mice are subjected to spinal cord injury and the clinical and neuropathlogical alterations in them compared to those observed in the cord injured wild type mice. We predict that the lesions in the immunodeficient mice will be far smaller and the animals will manifest less elements of paralysis. In the next step, we will again determine if therapy with erythropoietin will further block the smaller lesion characteristic of the immunodeficient mouse, and also protect the immunodeficient animals from severe paralysis.

In the final series of experiments, we will determine if activated T cells called in from the blood stream contribute to the severity of the injury at the site of trauma. To test this hypothesis, we will obtain naïve T cell lymphocytes from the spleen of normal unharmed wild mice. The naive cells will be rapidly purified and injected by IV into the immunodeficient RAG1 -*1*- mice. The animals will be rested for 24 hours and then an acute spinal cord injury will be induced. We predict that injured RAG1 -*1*- animals that have received wild type T cell lymphocytes will demonstrate much more paralytic illness, and a much larger zone of spinal cord injury. Selected groups of RAG1 -*1*- mice that have received the wild type T cells will be treated with erythropoietin and the effect of erythropoietin therapy on traumatic spinal cord injury in this adoptive transfer experiment will be quantified.

In addition to measuring the effect of erythropoietin on clinical paralysis and histopathology of the injured spinal cord, we will employ high resolution novel MR imaging techniques using labeled immune cells, (T lymphocytes) and intravenous gadolinium on living animals to further assess by MRI the mechanism of tissue injury and the effectiveness of the test therapy on traumatic spinal cord injury.

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PRINCIPAL INVESTIGATOR – **Frank V. Castello, M.D**.
Clinical Science Proposal
Grant Award - $267,498

Proposal Title: The Effect of FES on Children with Spinal Cord Dysfunction

Loss of the ability to walk due to spinal cord dysfunction has profound effects on patients, both physically and psychologically. Physical complications include a significant loss of muscle mass due to lack of use and a significant reduction in bone mineral density resulting in severe osteoporosis, especially of the long bones of the legs. The psychological impact can be quite profound and result in a significant negative impact on sense of well-being and sense of control over one's life. One promising method found to reverse some of the complications associated with the loss of the ability to walk is Functional Electrical Stimulation (FES) of the lower extremities. Patients with lower extremity paralysis are placed on a stationary bicycle. Electrodes are placed on the thighs, hamstrings, calves, and other appropriate muscle groups and attached to a signal generator that systematically stimulates muscle contraction so that pedaling the cycle is achieved. While patients have no voluntary control of their legs, studies in adults indicate increases in muscle mass and bone mineral density, as well as in cardiovascular endurance. However, no studies have been done in children to examine these effects. We propose to examine the effects of regular exercise using FES in children who have lost the ability to walk due to spinal cord dysfunction on cardiorespiratory function, muscle mass, bone mineral density, and psychological well-being. It is believed that a regular program of FES exercise will improve cardiorespiratory function, and increase muscle mass and bone mineral density, making children less susceptible to fractures. Resultant decreased muscle atrophy is hypothesized to improve physical appearance and sense of control, leading to improved psychological well-being.

An initial medical evaluation, including baseline measures of cardiorespiratory function, muscle mass, and bone mineral density, will be done in order to assess the appropriateness of participation in the program. Twenty-four children will undergo 9 months of FES cycling using the ERGYS 2 system at Children's Specialized Hospital, 12 children during year 1 (Group 1) and 12 children during year 2 (Group 2). A time-lag design will be used, such that all 24 children will be recruited and given initial medical evaluations in year 1. During year 1, Group 2 children will be given the physiological and psychological measures at the same time as Group 1 children. This will provide a control group with which to compare the effectiveness of the treatment in the Group 1 participants. Children will be monitored for blood pressure, heart rate, and complaints of fatigue while cycling. Subsequent measures of cardiorespiratory function, muscle mass, and bone mineral density will be measured every 3 months during participation in the study and at the end of the 9 months. Both child and parent reports of child psychological wellbeing related to emotional functioning, social functioning, and school functioning will be collected on the same schedule as the measures of cardiorespiratory function, muscle mass, and bone mineral density. Data analysis will investigate the change in cardiorespiratory function, muscle mass, bone mineral density, and psychological wellbeing given time (baseline, 3, 6, and 9 months) and age. Also considered will be the child's weight and year's post onset of injury or disease, the number of sessions, and the maximum workload achieved during exercise. Data analysis also will compare changes in these measures in the control group compared to the initial treatment group. If there are differences such that the initial treatment group is significantly better than the control group, we will have evidence of the effectiveness of the intervention. We then will be able to combine Groups 1 and 2 in a pre- vs. post-treatment comparison, increasing the number of subjects.

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PRINCIPAL INVESTIGATOR – **Ronald P. Hart, Ph.D.**
Basic Science Proposal
Grant Award – $185,573

Proposal Title: Differentiation of Therapeutic Stem Cells Using Micro RNAs

Stem cell transplants represent a new and promising therapy for curing chronic spinal cord injury. However, little is known about what may control the fate of these transplanted cells. Without control of cell fate, stem cell transplant may produce tissues that are inappropriate for the environment of the spinal cord at worst or non-functional in spinal cord recovery at best. A new class of genes, micro RNAs, has been identified in the past few years. These genes produce very small RNA molecules that control the production of specific proteins in the cell. We and others have found that there are stem cell-specific populations of micro RNAs, and that these populations change during differentiation. Others have demonstrated that artificially changing a single micro RNA restricts the differentiation of precursors into adipocytes. Based on this observation, we believe that specific changes in micro RNAs will restrict differentiation of transplanted stem cells into selected cell types. If this is true, stem cells may be "programmed" prior to transplant in order to produce the most effective cell type, such as oligodendrocytes to enhance remyelination.

Towards this goal, we will characterize the micro RNA expression patterns in stem cells that have been effective in promoting spinal regeneration. Once we have identified micro RNAs that change during differentiation, we will test if these micro RNAs can restrict differentiation in culture. This is a novel approach to the use of transplanted stem cells as therapies for chronic spinal cord injury since it may allow the "programming" of cells prior to transplant.

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PRINCIPAL INVESTIGATOR – **Hosea F. S. Huang, Ph.D.**
Basic Science Proposal
Grant Award - $390,602

Proposal Title: Preservation of Sperm Functions after Spinal Cord Injury

Over 80% of the individuals who survive spinal cord injury from all causes are men in the prime of their reproductive years. These men usually become infertile because they can no longer produce normal spermatozoa, perhaps due to abnormalities in their testicles. We have demonstrated that there are multiple causes which are responsible for these defects. With the support of the New Jersey Commission for Spinal Cord Research, we have investigated the relationship between the extent of cord injury and sperm function by using rats whose spinal cords were injured by surgical cutting or dropping of a rod from different heights directly onto the spinal cord. The results of these experiments demonstrated that sperm production persisted in these rats, but their sperm cannot move normally. The changes in sperm function appeared to be related to the degree of cord injury. This result is similar to that in SCI men in that they usually continue to produce sperm, but the sperm cannot move normally. We will continue to use these animal models to investigate the causes of abnormal sperm function after spinal cord injury, and test different treatments to improve sperm functions. Results of our previous experiments indicate that a series of biochemical processes that depend on a chemical called cAMP, referred to as "cAMP signaling cascade", in the testes and sperm became abnormal after spinal cord injury. We postulate that this is one of the major reasons that sperm of spinal cord injured men can no longer be fertile. In this new project, we will perform multiple experiments to determine the steps in this "cAMP signaling cascade" that are affected by spinal cord injury, and how these changes affect sperm functions.

We also will test the possibility of using antioxidants, vitamin E and selenium, to prevent the effects of spinal cord injury on sperm function. The results of these experiments will tell us the major reasons for abnormal sperm function after men have suffered spinal cord injury. We will then be able to develop s method to treat these men so that they can produce normal spermatozoa and become fertile again. If successful, such treatments will offer a simple and inexpensive therapeutic option to restore or preserve sperm functions after spinal cord injury, and will provide a low cost alternative to costly in vitro fertility technologies to restore reproductive capability of SCI men.

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PRINCIPAL INVESTIGATOR – **Randall D. McKinnon, Ph.D.**
Basic Science Proposal
Grant Award – $360,690

Proposal Title: Netrin Directed Glial Migration

The failure of regeneration in injured spinal cord is due in part to inhibitory molecules in myelin, the insulating sheath that wraps around neuronal axons to enhance axonal conduction. It is only after axonal connections are established that myelin forming cells (oligodendrocytes) populate the axonal tracts, and the normal function of these inhibitors may be to prevent axons from branching out and making new, inappropriate connections. This then may explain why the injured adult spinal cord is not competent at regeneration, as any myelin present prevents axons from regenerating. This also identifies targets for therapeutic intervention, and one approach under intense study is to block the interaction of myelin inhibitory molecules with their axonal receptors in the injured spinal cord.

An alternative strategy which we will explore is to create an environment at the wound site that more closely approximates the cellular composition of early development. Specifically, we wish to remove myelin competent oligodendrocytes while axons attempt to regrow, and then subsequently allow these cells to repopulate the repair site for remyelination. If this strategy only modestly improves axon regeneration it will advance the current status of therapeutic intervention. Our general strategy will employ growth factors (FGF and PDGF) to promote oligodendrocyte motility, and a directional cue (netrin) to direct traffic. The specific studies outlined in this proposal focus on the efficacy of the directional cue netrin.

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PRINCIPAL INVESTIGATOR – **Melitta Schachner, Ph.D.**
Basic Science Proposal
Grant Award – $317,768

Proposal Title: Genes Involved in Spinal Cord Regeneration in Zebrafish

Regeneration of neurons following spinal cord injury is generally believed to be inhibited by the glial scar at the site of injury, the generally inhibitory tissue environment of the adult central nervous system, and the intrinsic inability of some neuronal cell types to regrow their processes (axons and/or dendrites) after injury. In mammals, and in particular, humans, the glial scar and the inhibitory tissue environment are major impediments to neuronal regrowth and motor and sensory recovery after trauma. However, in zebrafish, a recognized biological model system benefiting from detailed genetic studies, neurons are able to regenerate and recover function after spinal cord injury, suggesting that the inhibitory elements characteristic of the adult mammalian central nervous system do not predominate.

Our research has demonstrated that spinal cord injured zebrafish indeed regenerate specific neuronal tracts, and that this regeneration requires the neuronal expression of an adhesion protein named L 1.1 that makes cells interact in a beneficial manner to foster regeneration. We believe that other genes are required for regeneration of neurons. Since we can dissociate the intrinsic neuronal growth from inhibitory tissue cues in zebrafish, we can easily identify regeneration-associated genes in neurons. Furthermore, some neuronal tracts regenerate (such as NMLF) and some do not (Mauthner cells). We can compare individual cells collected by laser capture microdissection from these two brain regions to select genes associated with successful regeneration. We will use DNA microarrays to identify specific genes expressed in successfully regenerating neurons and not in non-regenerating neurons. Our past studies with L 1.1 also demonstrate that we can block putative regenerative genes by adding morpholino antisense DNA molecules to injured spinal cords. These methods will allow us to demonstrate that a gene selected for its presence in regenerating neurons participates in the regeneration process. These studies will identify new cellular processes that are necessary for regeneration. In complement with newly developed therapies to reverse inhibition in the central nervous system of mammals, the newly identified regeneration-associated genes represent attractive new targets for drug development or gene therapy in humans.

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FELLOWSHIP GRANT RECIPIENTS:

PRINCIPAL INVESTIGATOR – **Tanya E. Borsuk**
Graduate Student Fellowship
Grant Award - $60,000

Proposal Title: QTL Mapping and Phenotypic Analysis of Dreher Suppressing Modifying Loci

Our research focuses on the production of neurons in the spinal cord. Specifically, we are interested in a structure called the roof plate, which forms in the spinal cord upon neural tube closure, and is responsible for secreting a multitude of signaling molecules that control the proper production of neurons in the dorsal spinal cord. By studying a mouse called dreher, a spontaneous mouse mutant that lacks completely a roof plate, we can gain a better understanding of how and when neurons are generated in the spinal cord. We have previously shown that the loss of the roof plate in the central nervous system has profound effects on the dreher mouse, including a disruption in both the pattern and generation of neurons in the spinal cord, as well as behavioral abnormalities in dr/dr adults, including hyperactivity and motor uncoordination. The use of the dreher mouse thus provides us with an important genetic tool to study the role that the roof plate plays in neuronal production in the spinal cord, and the development of the central nervous system.

We've recently identified a type of dreher mouse that displays less severe effects in the adult (less hyperactive, loss of ataxia). This phenomenon can be attributed to areas in this mouse's genome that are somehow suppressing the mutation. Through the identification of these genetic areas, we hope to gain further knowledge into the pathways that lead to the production of the roof plate and its secreted factors, and how they control the generation of neurons in the spinal cord. For spinal cord regeneration research to advance, more knowledge needs to obtained on exactly how neurons are generated, and how to instruct stem cells to a spinal cord lineage so that they can differentiate into functional neurons. Exposure of stem cells to developmentally important signaling molecules has led to partial recovery, and these results suggest that exposing stem cells to additional developmental factors could result in even greater functional recovery.

Further research on the mechanisms behind the suppression of the dreher mutation will benefit spinal cord research in two ways. First, it will increase our existing knowledge on how the roof plate and its secreted signaling molecules control the production of neurons in the spinal cord. Second, the identification of new pathways or signaling molecules involved in the production of neurons in the spinal cord can result in knowledge necessary to develop new techniques in the fields of stem-cell based therapies seeking to regenerate missing or damaged spinal cord neurons following disruption or trauma.

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PRINCIPAL INVESTIGATOR – **Ahryon Cho**
Graduate Student Fellowship
Grant Award - $60,000

Proposal Title: The Role of FK506-Binding Protein 8 in Mammalian Neural Patterning and Axon Guidance

The mammalian central nervous system consists of the brain and spinal cord. One important function of the brain is to process outside information from the rest of the body and to control the actions of the body. As the spinal cord mediates communication between the brain and the rest of the body, damage to the spinal cord disrupts the connection, which most often results in some form of paralysis. Spinal cord injury (SCI) was thought to be irreversible because the distinct neuronal subtypes are spatially organized with respect to their functions during early development of the spinal cord. Those cell types and their functional connectivity are not normally regenerated in the adult. However, novel therapeutic approaches are currently being developed, holding great promise for the functional recovery from SCI. One example is transplantation of specialized neural cells grown in the laboratory into the damaged spinal cords of SCI patients. The grafted neural cells can repopulate the injured spinal cord and restore functional neural circuits.

For the purpose of tissue engineering, it is important to find ways to produce large numbers of particular neuronal cell types from embryonic stem cells (ESCs), which have the capacity of becoming many different cell types. Recent studies showed that ESCs in the culture dish become specific cell types of the spinal cord under the same instructive cues used during developmental processes in the body. Sonic hedgehog (Shh) is one such cue in mammals: in early development, cells in the spinal cord determine their fates or subtypes in Shh concentration-dependent manner. However, tight control of the Shh-mediated neuronal differentiation is required for generating large, homogeneous populations of particular neuronal cell types that can be used for transplantation. Despite the potential usefulness of Shh for such therapies, the way it acts is not well understood. Thus, in order to get a better idea about how we can control Shh signaling with precision, we must uncover its mode of action.

For this reason, I will investigate the role of FK506-binding protein 8 (FKBP8), a novel component of Shh pathway. Our preliminary data show that FKBP8 acts like a brake on the Shh signaling machine; when FKBP8 functions, cells will respond only when they are exposed to Shh, but when FKBP8 function is disrupted, cells will respond whether or not Shh is present. Based on these findings, I will explore the role of FKBP8 in the spinal cord under this fellowship. First, I will continue and extend my ongoing genetic analysis of FKBP8 to better place it within the Shh pathway and determine the roles for FKBP8 in late neural development. Second, I will investigate the biochemical mechanism by which FKBP8 works as a negative regulator of the Shh pathway. Finally, I will test the role of FKBP8 in guiding embryonic stem cells to adopt the fate of specific neurons in the spinal cord. I hope that my research will help optimize transplantation therapies for SCI.

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PRINCIPAL INVESTIGATOR – **Margaret Julius**
Graduate Student Fellowship
Grant Award - $60,000

Proposal Title: A Novel Micromechanical Method for Controlling Microstructure in Nerve Grafts

Schwann cells are cells found in the peripheral nervous system that enhance spinal cord regeneration when incorporated into nerve grafts, also called guidance channels, implanted at the site of spinal cord injury. Until very recently, the therapeutic potential of this approach was limited by the fact that regenerating neurites entered the graft, but had difficulty exiting it to complete the regeneration process beyond the injury site. However, in 2004, Dr. Mary Bunge's group at the University of Miami published a new protocol that successfully enhances regeneration beyond the Schwann cell graft. With this major advance, it is timely to focus on optimizing the environment within the graft to maximize regeneration. Guidance channels are filled with a scaffold material, typically containing extracellular matrix components, through which the regenerating neurites grow. Several studies have shown that appropriate microstructural features of this scaffold enhance neurite outgrowth. One successful approach has involved the use of extracellular matrix gels whose fibers are oriented parallel to the axis of the guidance channel. It is believed that the effects of this fiber orientation are further amplified by the alignment of Schwann cells with the fibers, providing a clear path for the neurites to grow along through the channel. If this is true, then straightforward protocols for orienting the scaffold material will be an advantage in further optimizing Schwann cell nerve grafts. However, the method previously used to orient extracellular matrix gels, exposure to a high-strength magnetic field, involves a specialized facility that is not widely available to others who might wish to pursue this approach.

This proposal seeks to establish an alternative method based on the use of very fine gauge needles, with diameters on the order of 100μm. Studies have shown that connective tissue fibrils attach to and orient around acupuncture needles of this size, thus creating a field of tissue alignment along the needle axis. If a similar phenomenon occurs in extracellular matrix gels, which have a similar composition to the extracellular matrix component of connective tissue, this would provide a simple, accessible means of orienting the gel. To test this hypothesis, we will first establish a methodology for the use of micromechanical needling to orient two different gel systems, collagen and fibrin, both of which are used in guidance channel construction. The oriented gel configurations produced in this way will then be tested for their ability to guide Schwann cells into an oriented arrangement within the guidance channel. These pre-oriented Schwann cell grafts will be tested in future work for their ability to enhance neurite regeneration, both in vitro and in animal studies. This project matches the first item listed in the NJCSCR funding priorities, "studying strategies to promote neuronal growth and survival."

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PRINCIPAL INVESTIGATOR – **Hyuk Wan Ko**
Postdoctoral Fellowship Grant
Grant Award - $100,000

Proposal Title: The role of Ciliagenesis and Cell Cycle Phase in Hedgehog Signaling During Embryonic Stem Cell Differentiation

Recent studies showed that transplantation of embryonic stem cells may restore the loss of neurons and glial cells in a model of spinal cord injury. Because ES cells can be easily maintained, propagated, and genetically manipulated, they hold great promise as a source of specialized cell types for therapeutic approaches in treating and curing spinal cord injury. However, less than 10% of an entire population of transplanted embryonic stem cells differentiate into neurons. Therefore, one of the major challenges in cell therapy is to develop reliable protocols for differentiation of embryonic stem cells into specific types of neurons and glia in culture prior to transplantation.

In this proposal, I investigate the mechanism by which embryonic stem cells differentially respond to cell fate-inducing signals to become specialized types of spinal cord cells. Our laboratory is using mouse genetics and cell biology to approach issues such as this. Recently, our lab and another group identified a novel mechanism required for controlling cell fate during spinal cord development. This mechanism, called intraflagellar transport, is intimately tied to the way cells respond to a signal called "Hedgehog", which controls neural cell fate. Most mammalian cells use the intraflagellar transport mechanism to produce a highly specialized structure at the cell surface called the primary cilium. The role of primary cilia in most cell types has remained mysterious, although recent data suggest they may playa role in cell-cell signaling. Indeed, various mutations that alter intraflagellar transport activity affect the ability of cells to produce primary cilia, but also change the way they interpret and respond to Hedgehog signals. While most cell types generate a primary cilium, they do so only during certain phases of cell cycle, suggesting that response to Hedgehog signals may also be tied to the phase of the cell cycle.

I will carry out experiments to investigate the role of primary cilia and the cell cycle in the way embryonic stem cells respond to Hedgehog signals as they differentiate into various neural cell types. I will use different mutant strains of mice that are defective in the formation of primary cilia to test the function of these structures in embryonic stem cell differentiation. I will also test the hypothesis that developing cells might respond differently to Hedgehog signals in different phases of cell cycle. I will approach these issues using a combination of genetic, molecular and cell biological techniques. From this study we can better understand how embryonic stem cells interpret positional cues with respect to their cellular context to tightly regulate the types of neurons produced from these cells. This work should help us to design efficient protocols for tissue engineering that would be required for successful transplantation therapies in the treatment of spinal cord injury.

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