NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH

2006 B CYCLE

DIRECTORY OF GRANT AWARDS FOR SPINAL CORD INJURY AND DISEASE RESEARCH

DECEMBER 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 2006 B 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/

2006 MEMBERSHIP INFORMATION

Steven M. Reich, M.D., Chairperson
Cynthia Kirchner, M.P.H., Vice Chairperson
Peter W. Carmel, M.D.
John D. Del Colle
Susan P. Howley
Henry R. Liss, M.D.
Patricia Morton, Ph.D.
Mark L. Pollard
Scott A. Whitman

COMMISSION PERSONNEL

Gabriel Milton, Executive Director
Christine Traynor, Administrator
Mary Ray, Fiscal Manager

NEW JERSEY COMMISSION ON SPINAL CORD RESEARCH GRANT AWARDS

ONE-TIME GRANT FOR START-UP COSTS RECIPIENT:

PRINCIPAL INVESTIGATOR – Treena Arinzeh, Ph.D.
Grant Award: - $686,463

Proposal Title: **Neuronal Differentiation of Stem Cells on Nanomeshes**

In the United States, there are approximately 250,000 people living with spinal cord injuries, and 11,000 new injuries are reported every year. The principal repair strategy is to entice new axonal pathways to regenerate across the spinal cord lesion. Despite many promising studies, regenerating a sufficient amount of axons over long distances to restore function has yet to be achieved. Replacing the damaged tissue with nerves taken from other anatomic sites or allograft material is one option, but the best hope for complete or nearly complete recovery is to coax the damaged nerves to regrow. Schwann cell-laden grafts and nerve conduits have shown promise for repairing nervous tissue and optic nerves, as have injections of adult stem cells, but the size and complexity of the spinal cord warrants the development of specialized constructs combining several technologies. The emerging field of tissue engineering specializes in combining structural and functional biomaterials, appropriate cell types, protein delivery and/or genetic manipulation. Accordingly, tissue engineering holds great potential to become the optimal approach for the repair of the spinal cord. At the forefront of investigation is the use of stem cells because of their ability to turn into various cell types and thus, promote the regeneration of the damaged or diseased tissue of interest. Mesenchymal stem cells (MSCs) are cells that have been shown to turn into several different cell types. MSCs, which are obtained from adult bone marrow and expanded in cell culture, are believed to be valuable as a readily available and abundant source of cells in the tissue engineering field. However, for spinal cord injuries, MSCs need to be combined with an appropriate scaffold material that, at a minimum, supports attachment, their ability to turn into neurons, and promote neurite extension in a controlled fashion. For this technology to advance into clinical application, the development of improved scaffold materials is needed.

The goal of this research program is to develop an optimal transplantable nerve construct by investigating biomaterial structures and geometries that promote stem cells to turn into neurons and guide axon regeneration across the construct. We will determine the effect of the fiber diameter, orientation, and chemistry of non-woven fibrous scaffolds on stem cells turning into neurons. We hypothesize, based on preliminary findings, that scaffold design, specifically nano vs. micron size fiber diameters, affects cell shape, and will subsequently affect function and their ability to turn to neurons. We will examine neuronal differentiation of human MSCs on nano vs. micron fiber scaffolds having the compositions of poly l-lactic acid (PLLA) and 75:25 poly lactic co-glycolic acid (PLGA). The percentage of cells expressing neuronal cell characteristics will be determined. Neuron function will also be determined by electrophysiology techniques. We will also determine the effect of orienting the fibrous scaffolds on stem cell behavior to test the hypothesize that oriented fibers will promote neurite extension and alignment.

Contact Information:
Treena Arinzeh, Ph.D.
New Jersey Institute of Technology
University Heights
323 Martin Luther King Jr. Blvd.
Newark, NJ 07102
973-596-5269
arinzeh@njit.edu

INDIVIDUAL RESEARCH GRANT RECIPIENTS:

PRINCIPAL INVESTIGATOR – Monica Driscoll, Ph.D.
Basic Science Proposal
Grant Award – $400,000

Proposal Title: **Genes Contributing to Necrotic Death of Injured Neurons**

We will molecularly describe three genes critical for neuronal necrosis and determine how their disruption blocks neuronal death in a simple animal model; we will test how cell death genes effect regeneration of severed neurons. In spinal cord injury some neurons are directly damaged, but many others die during a phase of secondary necrosis induced by exacerbated ion channel activity in response to signals inappropriately released by injured neurons. Blocking or delaying secondary neuronal necrosis would significantly limit debilitating consequences of injury, but a more detailed understanding of the molecular mechanisms of necrosis is required for design of novel and effective therapies. A central goal of our work is the identification of genes critical for the progression through necrosis induced by ion channel-inflicted neuronal injury. We are exploiting uniquely applied genetic approaches in the *C. elegans* model system to identify necrosis suppressor mutations. In general, certain experiments that are implausible or impractical in higher organisms can be conducted rapidly, cheaply, and with cleanly interpretable results in *C. elegans*. Since most basic biological processes, including cell death, are conserved from nematodes to humans, we can identify critical molecules and decipher the basic molecular rules of a given process in *C. elegans* and then use this information to address the function of related molecules (homologs) in humans. Our underlying working hypothesis is that molecular elaboration of necrosis mechanisms in *C. elegans* will identify key molecules needed for the progression through necrosis in humans. Disruption of these human genes or inactivation of their protein products are highly plausible strategies to block the devastating consequences of the waves of necrosis that follow initial injury.

Our first aim is to determine the molecular identities of three necrosis suppressor genes, to determine how these genes act in the necrosis pathway, and to test if mammalian versions of these genes can exert the same function in nematodes (indicating conserved activity). This work is important because we will identify novel molecules that contribute in significant ways to the necrosis that accompanies injury. Since the molecules identified are likely to be similar in nematodes and humans, the data we generate can allow intelligent design of much-needed effective intervention therapies. Our second aim focuses on advancing understanding of the basic biology of neuronal regeneration, another key goal in spinal cord injury research. A recent breakthrough has shown that *C. elegans* motorneurons can regenerate and reform functional connections after having been severed by laser microsurgery. We plan to address how eliminating specific types of neuronal death (injury-associated necrotic death, apoptotic cell death, and autophagy, which involves self-consumption) influences the efficiency of regeneration and functional reconnection. Our planned experiments will constitute the first systematic survey of how three different death processes influence regeneration of single axons in a fully physiological context. The anticipated outcome, a clear answer on how modulating death pathways within injured cells can influence reconnection, is of basic importance to fundamental issues in recovery from spinal cord injury.

Contact Information:
Monica Driscoll, Ph.D.
Rutgers, The State University of New Jersey
Department of Molecular Biology & Biochemistry
604 Allison Road, A 232 Nelson Biological Laboratories
Piscataway, NJ 08855
732-445-7189
driscoll@waksman.rutgers.edu

PRINCIPAL INVESTIGATOR – Martin Grumet, Ph.D.
Basic Science Proposal
Grant Award - $308,593

Proposal Title: **Isolation of NSC from ES Cells & Applications in SCI**

To optimize isolation of neural stem cells for transplantation to improve recovery from spinal cord injury. Embryonic stem (ES) cells are versatile cells that hold great promise for human therapies for many disorders. An additional important advantage of ES cells as a potential source of neural stem cells is the possibility of establishing banks of cells with a wide range of types for transplantation which would enable donor cells to closely match recipients, thereby reducing problems of rejection. This proposed research will optimize methods for preparing neural stem cells from ES cells. Recent research suggests that neural stem cells can be derived from these ES cells. Neural stem cells are multipotent giving rise to various types of cells including neurons and glia. It is believed that these neural stem cells will be useful for the treatment of nervous system disorders and our preliminary data support this idea. For example, transplantation of neural stem cells into the injured rat spinal cord has shown modest improvement in recovery. We are focusing on neural stem cells because our research indicates that acute transplantation of radial glial neural stem cells (RG3.6 cells) improved recovery following spinal cord injury (Hasegawa et al., 2005). Neural stem cells can become various types of cells in the nervous system including neurons that transmit signals through their axonal cables, astrocytes, and oligodendrocytes that form the myelin which insulates axons to ensure signal conduction through nerves. Two major functional consequences of spinal cord injury are the loss of nerve cables and scar formation which inhibits nerve regrowth. We found that acute transplantation of RG3.6 cells mitigated each of these detrimental processes. These results suggest that secondary damage following spinal cord injury can be reduced by transplanting neural stem cells.

Our first goal is to determine whether different types of neural stem cells have the ability to protect against secondary damage. We will compare the protective effects of RG3.6 cells with different types of neural stem cells including those isolated from ES cells after acute transplantation into rats with spinal cord injury to determine which are most effective in preventing loss of nervous system function. A second goal is to explore the possibility that neural stem cells transplanted soon after injury not only protect the spinal cord from secondary damage but also later become oligodendrocytes which restore lost myelin and further improve functional recovery. Since oligodendrocytes can be differentiated from ES cells, we believe that they become neural stem cells during this differentiation. Therefore, we will explore approaches to direct neural stem cells to differentiate into oligodendrocytes after transplantation. We already have evidence that we can cause neural stem cells to become oligodendrocytes in a delayed manner. Mature oligodendrocytes transplants have not been effective because the oligodendrocytes need to differentiate in the spinal cord to myelinate effectively. Therefore, we will test factors that will induce neural stem cells to become oligodendrocytes in the spinal cord after transplantation. The goal of this research is to optimize the use of ES-derived neural stem cells to limit damage and promote recovery after spinal cord injury. We expect that many of the methods and reagents optimized in this proposed project with rodent cells will be applicable to human ES and neural stem cells and will facilitate their isolation for use in clinical trials.

Contact Information:
Martin Grumet, Ph.D.
Rutgers, The State University of New Jersey
W. M. Keck Center for Collaborative Neuroscience
604 Allison Road, D-251
Piscataway, NJ 08854
732-445-6577
mgrumet@rci.rutgers.edu

PRINCIPAL INVESTIGATOR – Troy Shinbrot, Ph.D.
Basic Science Proposal
Grant Award - $199,734

Proposal Title: **Combined *In Silico-In Vitro* Optimization of Spinal Implant Migration**

We seek to quantify how neuronal connections must be guided so as to restore function in prospective regenerative therapies. On average, one serious spinal cord injury occurs every day in New Jersey*. There is no sensible way to calculate the human cost of these injuries. The lifetime financial cost for caring for these citizens – most of whom are younger than 40 – ranges from half a million dollars to over $2 million dollars depending on severity.** At an average cost of a million dollars in new obligations every day, this is clearly a problem worthy of significant public attention.

Numerous laboratories worldwide are consequently actively engaged in pharmacological, neuroprotective, surgical and stem cell therapies intended to promote regrowth of neurons following spinal cord injury (SCI). In this proposal, we observe that although existing efforts to regenerate spinal neurons are crucial to the restoration of function following SCI, they are not by themselves sufficient. In order to achieve the goal of functional recovery, regrowing neurons must in addition find a way to reach specific and appropriate target locations - if neurons do not reach the right targets, they simply will not restore function.

In this proposal we show that because of the complexity of spinal connections, the *a priori* chance of a nerve axon reaching a specified target in the spinal column without guidance can be expected to be less than one in a million. We believe, however, that an integrated program of computational simulations combined with biological experiments can identify guidance strategies that will successfully steer regrowing neurons so that their processes will reach usable targets and thereby restore function. In future therapies, these guidance strategies would consist of injecting specified chemical agents into particular locations in the spinal cord to provide 'traffic signals' that would effectively ensure that regrowing neurons make functional connections. Without these signals, neurons – like cars – would have no way of choosing one destination over another.

We propose to attack this problem by bringing together a cross-disciplinary collaboration of computational modelers experienced in neuronal growth analysis with nerve tissue engineers and a material scientist with expertise in tissue culture on microfabricated substrates. This work will produce an experimentally validated, predictive model for neuronal growth that will inform future therapeutic interventions by providing specific and concrete data on where injections of guidance cues, and of what type, must be introduced to ensure that regrowing neurons make connections that successfully restore sensory and motor function following SCI.

---

*Center for Disease Control Spinal Cord Injury Fact Sheet: http://www.cdc.gov/ncipc/factsheets/scifacts.htm
**NJ Dept. of Health & Senior Services Update, Healthy New Jersey 2000, Second Update and Review http://www.state.nj.us/health/chs/yr2000up/injuries.htm

Contact Information:
Troy Shinbrot, Ph.D.
Rutgers, The State University of New Jersey
Department of Biomedical Engineering
98 Brett Road
Piscataway, NJ 08854
732-445-6710
shinbrot@soemail.rutgers.edu

PRINCIPAL INVESTIGATOR – Sue Ann Sisto, Ph.D.
Clinical Science Proposal
Grant Award - $397,210

Proposal Title: **Shoulder Pain/Injury Due To Wheelchair Propulsion in SCI**

Due to paralysis of their legs, many individuals with spinal cord injury (SCI) are forced to rely extensively on their arms for mobility. Unfortunately, the repeated performance of upper limb weight-bearing activities like manual wheelchair propulsion places a great deal of stress on the shoulder joint, putting it at significant risk for overuse injuries and pain. Shoulder pain is a common secondary medical complication associated with SCI, especially those with tetraplegia, with prevalence between 31%-73%. Since many people with SCI are dependent on their upper limbs for independence, some have gone as far as to say that injury to the shoulder may be functionally and economically equivalent to a SCI of a higher neurological level. At the Kessler Medical Rehabilitation Research and Education Corporation (KMRREC), Human Performance and Movement Analysis Laboratory (HPMAL), we have made great strides toward understanding the relationship between manual wheelchair propulsion and upper limb pain in individuals with SCI. Unfortunately, although a great deal of research has been done in individuals with paraplegia, very little has been done in those with tetraplegia.

Therefore, the purpose this study is to identify the factors during wheelchair propulsion that predict shoulder pain and injury in individuals with tetraplegia. We will achieve this by evaluating upper limb kinematics (joint motion), kinetics (joint forces), and muscle activity during wheelchair propulsion in individuals with tetraplegia. In addition, each individual will undergo a thorough evaluation for shoulder injury, including history and physical examination, shoulder X-rays, and MRI. By understanding the factors that cause shoulder injury and pain during wheelchair propulsion in individuals with tetraplegia, we will be better able to make specific recommendations related to wheelchair design, wheelchair prescription, wheelchair set up, and wheelchair propulsion training that have the potential to prevent pain and injury in this population.

Contact Information:
Sue Ann Sisto, Ph.D.
Kessler Medical Rehabilitation Research and Education Corporation
Human Performance and Movement Analysis Laboratory
1199 Pleasant Valley Way
West Orange, NJ 07052
973-243-6888
ssisto@kmrrec.org