

Winter 2010

THE PROJECT

A Publication of The Miami Project To Cure Paralysis & The Buoniconti Fund To Cure Paralysis

The Miami Project To Cure Paralysis



Research Review 2009



UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE



A message from the
Chairman and the
Scientific Director

Barth Green, M.D.,F.A.C.S.
W. Dalton Dietrich, Ph.D.



As we begin a new decade, The Miami Project Research Program is well positioned to identify and treat novel mechanisms of injury following brain and spinal cord injury and translate these discoveries to the clinic. Our scientists and clinicians conduct a wide variety of translational and clinical research that is already touching the lives of persons with paralysis due to central nervous system (CNS) injury. In the area of discovery, sophisticated screening approaches are identifying new treatments to protect against cell death as well as promote the regenerative capacity of the injured brain and spinal cord. Translational studies using clinically relevant animal models are providing encouraging results that are so important as we attempt to translate our studies to the clinic. Finally, clinical studies are completed or are currently underway that show that our discoveries can be successfully translated to people with both acute and chronic spinal cord injury. The Project is involved in single as well as multi-center trials that will change the way we treat people with paralysis.

In the area of cell protection, therapeutic hypothermia is making a big difference in people's lives with some type of CNS trauma. Following traumatic brain injury, hypothermic therapy is being used to reduce elevations in brain pressure and temperature that can cause serious secondary insults to the nervous system following the initial trauma. In people suffering from acute spinal cord injury, cooling strategies have

also been shown to be safe and effective. In both cases, therapeutic hypothermia is being directed toward clinical trials in larger populations to determine safety and efficacy. These examples of successful translation of laboratory findings to the clinic emphasizes the importance of our interdisciplinary program in terms of developing new treatments for brain and spinal cord injury.

In the area of regenerative medicine, The Miami Project researchers are advancing human Schwann cell transplantation strategies to target both acute and chronic spinal cord injury. Pre-clinical (animal) work has shown that these cells can both protect and promote recovery of function even when administered in a delayed fashion after spinal cord injury. The ability of Schwann cells to remyelinate, or reinsulate, damaged axons appears to be a clinically relevant target for reparative therapy. Work continues in The Miami Project to obtain the necessary safety and pre-clinical data to facilitate an FDA approved trial in the near future. These studies are again based on basic science discoveries made by Miami Project scientists that are now being translated to the clinic.

In addition to neuroprotective and reparative strategies, our clinical scientists are significantly contributing to the quality of life of people living with paralysis due to spinal cord injury today. Exercise conditioning strategies to improve strength and skill as well as improve cardiovascular function and other consequences of aging are now being advanced, all of which have a positive impact on quality of life. Novel rehabilitation strategies including robotic assisted locomotion and whole body vibration as well as upper extremity rehabilitation approaches are also leading to improved function. Our vision to combine neuroprotective, reparative, and rehabilitation strategies to maximize recovery of function after brain and spinal cord injury is challenging but real.

A major aim of our program is to provide information and education to individuals that need to learn more about what research and clinical progress is being conducted in the spinal cord field. Thus, our Education Department is extremely active in providing critical information to individuals with paralysis as well as their loved ones who are seeking appropriate rehabilitation facilities, advice about unproven therapies, and other information regarding paralysis. Our faculty is training the next generation of scientists to conduct these extremely specialized studies to continue to advance this scientific field. Training of graduate students, postdoctoral fellows, and visiting scholars is therefore an important component of our overall program.

Over this past year, there has been a continued smooth translation of our discoveries to the clinic. Though the progress may seem long and slow at times, it is critical that the therapies we develop cause no harm. The Miami Project's researchers and scientists are collaborating with scientists and investigative groups throughout the world in terms of testing novel therapies targeting individuals with paralysis. In addition to moving our own discoveries to the clinic, we are also working with biotech and pharmaceutical companies to test new therapies in large numbers of subjects. These collaborations enable the entire field to move forward at a faster rate. This is an exciting time in the history of The Miami Project and we believe this coming year will be the most exciting ever. Our scientists and clinicians are truly blessed with the continued support of our many friends, individuals, foundations, and government agencies that are helping us achieve our goals. Thank you for this continued support, and we look forward to an even more exciting 2010.

W. Dalton Dietrich, III, Ph.D.
Scientific Director
The Miami Project to Cure Paralysis
Kinetic Concepts Distinguished Chair in Neurosurgery
Professor of Neurosurgery, Neurology, and
Cell Biology & Anatomy
Vice-Chair for Research, Neurological Surgery

Barth A. Green, M.D., F.A.C.S
Co-Founder and Chairman
The Miami Project to Cure Paralysis
Professor and Chairman, Department of Neurological
Surgery
Professor, Departments of Orthopaedics and
Rehabilitation Medicine

THE PROJECT

A Publication of The Miami Project To Cure Paralysis & The Buoniconti Fund To Cure Paralysis

RESEARCH REVIEW 2009

- 2 Message from the Chairman, Dr. Barth A. Green and Scientific Director, Dr. W. Dalton Dietrich
- 5 Fundraising, Administrative and Scientific Support Staff

FEATURE ARTICLE

- 6 Investigational New Drug Process

CLINICAL TRIALS INITIATIVE UPDATE

- 8 SCI and TBI Clinical Trials

RESEARCH HIGHLIGHTS

- 12 Whole-body Vibration
- 13 SCI Pain Research
- 14 Researchers Identify Protein Family Responsible for Regulating Nerve Regeneration
- 16 Similarities between MS and SCI
- 17 Director of Education Kim Anderson-Erisman, Ph.D. Gail F. Beach Memorial Lecture Series
- 18 Research Funding
- 20 Faculty Profiles
- 35 Distance Learning Program
- 36 Research Publications 2009



Editor & Contributor, Kim Anderson-Erisman, Ph.D.

Managing Editor, Scott Roy

Graphic Editor, Robert Camarena

Contributors, Maria Chagoyen-Audet, Diana Berning, Randy Carlson, John Bethea, Jon-Roi Vega

Photographs & Graphics, Robert Camarena, John Dietrich

Website: www.themiamiproject.org

Physical Address:

1095 NW 14th Terrace, R-48
Miami, FL 33136

Phone: 305-243-6001

Mailing Address:

Post Office Box 016960, R-48
Miami, FL 33101

The Project is published biannually by The Miami Project to Cure Paralysis, a Center of Excellence at the University of Miami Leonard M. Miller School of Medicine.

All contents ©2010. Reproduction in whole or in part without written permission is prohibited. The University of Miami is an Equal Opportunity/Affirmative Action Employer.

Privacy Policy: If you do not wish to receive **The Project** in the future, please send your request to the address above or call 305-243-7147.

The Miami Project scientific team is grateful for the dedication and hard work of the the fundraising, administrative, and scientific support staff. This incredible group of people spend countless hours providing direct clerical and administrative support to the research staff and raising the precious private funds to support Miami Project research endeavors.



Fundraising, Administrative, and Scientific Support Staff

Management

Marc A. Buoniconti
President

Suzanne M. Sayfie
Executive Director

Diana C. Berning
Administrative Director

Stephanie Sayfie Aagaard
Director, Major Gifts, Corporate Relations and Marketing, Events

Randy L. Medenwald
Director, Government Relations

Francine Y. Schoen, MLS
Director, Foundation Relations

Kim Anderson-Erisman, Ph.D.
Director, Education

Megan Hess
Director, Annual Giving

Bill Sims
Director, Operations

Teri I. Bendell, *Director*
Web Services, Auction and Database Management

Scott P. Roy
Director, Communications

Kristin Wherry
Director, National Chapters

Support Staff

Teresa Arcay
Rebecca Avshalom
Robert Camarena
Randy Carlson
Maria Chagoyen-Audet
Judith Cox
Georgina Escobar

Evelyn Gomez
Jenna Green
Jacqueline Hamilton
Jenissia Jeanty
Cynthia Jones
Michele Kenny
Jeremy Lytle

Jacqueline Manzano
Leonor Muros
Mirian Otero
Joanne Ponce-Aleman
Marcela Rojas
Tim Saltsman
Erica Sanabria

Maria Serna
Jacqueline Tommasino
Jon-Roi Vega
Postdoctoral Fellows 17
Graduate Students 17
Research Staff 87
Other Students 63

The Food and Drug Administration (FDA) may seem like an insurmountable hurdle to getting drugs, devices, and cellular therapies approved for treating many devastating diseases/conditions that the public faces, such as spinal cord injury (SCI) and traumatic brain injury (TBI). However, the mission of the FDA is to protect public health. To do this in a reliable and standardized manner, a step-wise process has been developed to take potential therapies from “**discovery-to-development-to-market**”. Basic science is the **discovery phase**. When an intervention shows promise in the laboratory, and the decision is made to develop and investigate its potential in humans, the **pre-clinical or non-clinical phase** begins. This early development phase is done in animals to demonstrate that the intended therapy is reasonably safe before proceeding with small scale human clinical studies. Depending on the complexity of the target disease/condition and the intended drug/device or biologic therapy, the pre-clinical phase can take 2-5 years. A critical part of this time involves the creation of relevant disease/condition models in animals. To determine safety for use in humans, toxicology studies, dose and delivery studies, and, for cellular therapies, biodistribution (movement to different organs) and tumorigenicity (possibility of forming tumors) studies are conducted in animals. When safety has been established, an Investigation New Drug (IND) application is submitted to the FDA requesting approval to begin a phase I study in humans. **Phase I** studies enroll a very small number of research subjects (in the 10's). The main goal (primary endpoint) is to determine safety. This is done by observing for adverse responses, monitoring for toxicity, and in most situations, also determining if the dose produces therapeutic activity. If the phase I study is successful, then a phase II study is proposed to the FDA. **Phase II** studies enroll more subjects (in the 100's) and include a control (placebo) group for comparison. The primary endpoint is also safety (by determining short-term risks), but preliminary determinations of producing a beneficial effect (efficacy) are the secondary endpoint. The next step is to conduct a phase III study. **Phase III** studies involve a large number of research subjects (1000's) and the primary endpoint is efficacy. These studies are also *controlled* (placebo group), *randomized* (subjects randomly assigned to either the drug/cell group or the placebo group), and *blinded* (the participants do not know which group they are assigned to). Phase III studies are considered “pivotal” because if they are successful a New Drug Application (NDA) can be submitted for final approval. However, if they are unsuccessful, the intervention can go no further in the process. It takes approximately 6-7 years to complete the development phases I-III studies and anywhere from 6

months to 2 years to obtain the approved NDA. Once the FDA approves the NDA for a particular drug/cell therapy, the intervention is then widely available to any individuals that qualify for it and it can be prescribed by physicians.



Anil Lawani, M.S.

The Miami Project has been hard at work to move the Autologous Schwann Cell Transplantation therapy for SCI through the FDA process. It was only in December 2007 that we decided to transition from the **discovery phase** to the **pre-clinical phase** for this therapy. We have made tremendous accomplishments in just 2 short years. An

important factor that facilitated the success and speed of all of those accomplishments was the hiring of **Mr. Anil Lalwani, M.S.**, as the **Project Manager**. Mr. Lalwani has over 15 years of experience in the biotechnology field, including Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Quality Systems Regulation (QSR), and FDA regulatory compliance. He is currently the Director of Biotechnology Resources at the University of Miami Miller School of Medicine and for the last year has dedicated 20% of his time to managing our Schwann cell therapy project. He also facilitated our pre-pre-IND discussion with the FDA and his experience and knowledge of regulatory affairs and project management has been essential to our navigation of the pre-clinical phase and will be even more critical as we prepare our IND application for submission to the FDA.

What is an IND? An IND can be considered a legal permit to test an unproven drug/cellular therapy in humans. This became federal law as a result of past unethical experimentation on humans (such as the Tuskegee Incident, Thalidomide Tragedy, World War II Nazi concentration camps). An IND application has the following three main components: 1) Animal pharmacology and toxicology studies; 2) Manufacturing and Controls information; 3) Clinical protocols and investigator information.

Under the guidance of Mr. Lalwani, we are deep in the process of our **animal pharmacology and toxicology studies** for the Schwann cell transplantation therapy. When we had our pre-pre-IND discussion with the FDA in August 2008, they stated specifically that they wanted to see data about toxicity, cell survival, migration of the cells to other body parts (biodistribution), and whether

We continue to make significant headway in preparing our **clinical protocol and investigator information**. We must provide a detailed outline of the investigation, taking into consideration differences between acute and chronic injury conditions. We must also include research subject screening criteria, safety exclusion criteria, a dosing plan and duration of the study, as well as a robust safety

REMAINING MILESTONES:

Complete toxicology & tumorigenicity experiments in rodent models

Complete GLP safety data collection & analysis

Invite Schwann Cell clinical trial External Advisory Board to Miami for meeting

Arrange pre-IND consultation with the FDA

Submit full IND application to the FDA

or not they formed tumors (tumorigenicity) in animals 6 months after the cells had been transplanted. We began these studies by utilizing our human Schwann cell product and transplanting it into rats. These studies require immunosuppression treatment, because the rat body recognizes human cells as foreign and tries to kill them, and have proven very difficult. We are currently conducting parallel experiments in which we are transplanting rat Schwann cells into rats. These studies do not require immunosuppression; however, we will need to demonstrate comparability between human and rat Schwann cells in our evaluations.

We have made quite a bit of progress regarding our **manufacturing and control information**. This includes very detailed information about the Chemistry, Manufacturing, and Control (CMC) of our human Schwann cell product. It requires a step-by-step description of how Schwann cells will be prepared in culture, after having been removed from a research subject in preparation for transplantation into the spinal cord injury site. Good Manufacturing Practices (GMP) must be followed and documented. To meet this requirement we have been working with colleagues at the [University of Miami's Wallace H. Coulter Center for Translational Research](#) where there is a GMP facility. We have also developed several Master Batch Records and Standard Operating Procedures (SOPs) defining how Schwann cells will be harvested, separated from the nerve, expanded in culture, purified, and prepared for transplantation. A list of product release criteria will be established, which must be met each time Schwann cells are prepared for transplantation into a research subject.

monitoring plan. Our remaining milestones are listed in the above box. It is imperative that we complete the toxicology and tumorigenicity experiments successfully in rodents. We will be holding a meeting with the External Advisory Board (EAB) for this study to seek their input on our pre-clinical data and clinical trial design. The EAB is a group of experts in SCI clinical trials who have no internal connection to The Miami Project (i.e. they are unbiased). Their guidance will be crucial to obtain prior to submitting our IND application. Proper trial design is very closely linked to the success of the trial. ***The last thing that the SCI field needs is another failed trial due to flawed design, so we are seeking as much input as possible ahead of time to prevent that from happening rather than rushing to the FDA with an ill-designed proposal.*** Once the clinical protocol is finalized, we will submit it to the University of Miami Miller School of Medicine Institutional Review Board (IRB) for human subject safety review. At the same time, we will arrange for a pre-IND consultation with the FDA. This will be our opportunity to ask the FDA any remaining questions prior to our submission of our IND application. After those questions are answered and we finalize our IND application, it will be submitted. It would not be out-of-the-ordinary for the IND application to be several thousand pages long; in fact, the IND application that Geron, Inc., submitted regarding stem cell use for acute SCI was 21,000 pages!

Overall, we are proud of the extensive progress we have made in only 2 years of pre-clinical development. The overriding factors guiding this process are safety and ethics. We thank the SCI community for their continued support as we continue to move forward! 🙌



Clinical Trials Initiative Update

2009 was an excitingly productive year for The Miami Project and its University of Miami Miller School of Medicine colleagues in Neurological Surgery and Rehabilitation Medicine. The Clinical Trials Unit, led by Allan Levi, M.D., Ph.D. and M. Ross Bullock, M.D., Ph.D., is up and running and actively involved with over 20 clinical trials involving spinal cord injury (SCI) or traumatic brain injury (TBI). The Clinical Trials Unit provides the infrastructure needed to secure funding, obtain and maintain regulatory approval, recruit participants, collect data, and analyze the outcome of each clinical trial.

Clinical Trials for SCI

Autologous Schwann Cells for Acute and Chronic SCI

One of The Miami Project's most anticipated human clinical trial initiatives is testing human Schwann cell transplants in humans with acute and chronic SCI. We are preparing our Investigational New Drug (IND) application so as to gain approval from the Food and Drug Administration (FDA) to begin a Phase I clinical trial to determine safety. Specifically, we are working on the following **pre-clinical processes**:

Communications with the FDA

The Miami Project has continued to utilize the services of regulatory consultants at Biologics Consultant Group, Inc. Because of their familiarity with the FDA's expectations, our consultants provided valuable guidance on the first documents we sent to the FDA to introduce our Schwann cell transplant project plan. They are well qualified to advise us on our project as they are experts in developing cell and tissue-based therapy products and are knowledgeable about the evolving area of regenerative medicine. Because of their continued advice, most recently received in December 2009, we are making significant progress in completing the pre-clinical processes necessary to support a successful IND application to the FDA in the future.

Human Schwann Cell Manufacturing Process

One required pre-clinical process relates specifically to how the Schwann cells are prepared for transplantation. To get enough cells to inject into the injury site, Schwann cells from the trial participant will be used to grow more of their own cells in culture dishes. We are legally required to follow Good Manufacturing Practice (GMP) when processing the cells to assure the safety and quality of the cells used for transplantation. This is **essential** for human subject safety.

Every batch of cells must meet the same standards. GMP is a standard recognized internationally that requires documentation of every aspect of the procedures, activities, and operations



Gagani Athauda dissecting human sural nerve

involved in manufacturing the cells. To become compliant with this standard, we continue to work with colleagues at the University of Miami's Wallace H. Coulter Center for Translational Research, where a GMP laboratory is already available. Miami Project staff have spent many hours in this laboratory receiving training from the Coulter Center staff on GMP procedures and establishing Schwann cell manufacturing steps for human cells that will meet the expectations of GMP for the FDA.

Human Schwann Cell Safety

Another pre-clinical process we must complete is a large group of animal studies to verify the safety of transplanting Schwann cells into the spinal cord injury site. These studies, conducted under conditions similar to GMP studies, will be performed in-house and then all the tissue will be outsourced to a GLP (Good Laboratory Practice) certified laboratory and will test whether human Schwann cells produce tumors or cause toxic reactions in rats with acute and chronic SCI. These **long-term safety experiments** to evaluate toxicology, biodistribution, and tumorigenicity are also **essential** to human subject safety and for our IND application to be reviewed successfully by the FDA.

Biomarkers for acute traumatic brain injury and spinal cord injury

Miami Project neurosurgeons are conducting these crucial observational studies to identify biological markers for early diagnosis of TBI or SCI. Currently, there are no simple blood tests that enable physicians to identify the presence and severity of TBI or SCI in the emergency setting. In these trials, cerebrospinal fluid and blood serum samples will be analyzed in people immediately post-injury and compared with brain injury/spinal injury severity and outcome. The goal of this study is to identify biomarkers of TBI and SCI to facilitate earlier diagnosis of TBI/SCI and, thus, earlier intervention and management.

North American Clinical Trials Network

The Miami Project and UM Department of Neurological Surgery have become a part of the North American Clinical Trials Network (NACTN). NACTN is a network of institutions that is developing the infrastructure, methods, and skilled personnel needed to conduct trials for SCI. Presently, the collaborative centers are collecting natural history data from newly injured people to determine the medical and rehabilitative outcomes and complications that occur in people receiving standard of care. Participants are evaluated for one year post-injury. This information will help determine the design of SCI clinical trials.

Pregabalin in chronic spinal cord injury

The Miami Project and UM Department of Rehabilitation Medicine are participating in a Phase III trial evaluating the effectiveness of a drug called Pregabalin in treating chronic neuropathic pain in people living with SCI. Pregabalin, also known as Lyrica, is an anti-convulsant that has already been approved by the FDA for the treatment of pain associated with Fibromyalgia. The current study is a randomized, double-blind, placebo-controlled, multi-center clinical trial (the gold standard of clinical trial design) to identify whether Pregabalin can reduce the neuropathic pain symptoms caused by SCI as well as reduce pain-related sleep interference, functional limitations due to pain interference, and other pain-related symptoms.

Riluzole for acute spinal cord injury

The Miami Project in collaboration with NACTN will also conduct a clinical trial of the drug Riluzole. Riluzole has been approved for use in people diagnosed with amyotrophic lateral sclerosis (ALS). When Riluzole was tested in preclinical experimental SCI, it had a neuroprotective effect by blocking sodium from entering damaged nerve cells, which may prevent them from swelling and dying. The Miami Project/UM has received IRB approval for this Phase I trial and will begin enrolling subjects once the sponsor (Department of Defense) has provided the final approval.

Rolipram for acute spinal cord injury

The Miami Project is conducting pre-clinical studies to identify the optimal methods for delivering Rolipram as a neuroprotective therapy for acute spinal cord injury. The goal of these studies is to determine the best dose, route, and timing of administration of Rolipram to achieve maximal tissue protection. These studies are producing critical data needed to submit an Investigational New Drug application to the Food and Drug Administration to request approval to begin a Phase 1/2 clinical trial to test Rolipram's safety and efficacy in acute human spinal cord injury.

Therapeutic hypothermia for acute spinal cord injury and traumatic brain injury

The Miami Project and UM Department of Neurological Surgery recently completed a Phase I clinical trial to learn if inducing hypothermia (cooling) within the first few hours of traumatic spinal cord or brain injury is neuroprotective and makes a difference in the severity of injury. When a person with a new injury is brought to the trauma center, doctors place a cooling catheter in a large blood vessel (vena cava) that allows them to cool the body a few degrees to 33 degrees Celsius (or 92 degrees Fahrenheit). The cooling

is maintained for a 48 hour period and then the participant is slowly re-warmed at 0.1°C per hour. The researchers followed the participants for one year to compare outcomes. The details of the cooling method have been published in the *Journal of Neurotrauma* and the details of the clinical outcomes have been accepted for publication in the journal *Neurosurgery*.

In addition to this single center trial, the neurosurgeons have launched an initiative to study hypothermia treatment for acute traumatic spinal cord injury (SCI) in a multicenter clinical trial. For hypothermia to become a standard in acute SCI care, a randomized, prospective trial involving multiple centers will be needed to prove that hypothermia is safe and effective. University of Miami neurosurgeons have submitted the trial proposal to the Neurological Emergencies Treatment Trials group (NETT) for consideration. The NETT is a network of 17 academic medical centers with emergency care clinicians available to conduct large multicenter clinical trials.

Clinical Trials for TBI***BOOST for acute traumatic brain injury***

Miami Project neurosurgeons recently received funding from the National Institutes of Health (NIH) to begin a Phase II clinical trial of brain tissue oxygen monitoring in people with severe TBI. TBI can lower the concentration of oxygen in brain tissue and this has been observed to be associated with poor functional outcome. This trial will use a brain oxygen monitoring device to guide clinical decision making for therapy. Participants will be randomized to therapy based on the current standard of care monitoring (intracranial pressure) or standard of care plus brain oxygen monitoring. The results will be used to develop a pivotal Phase III trial to test the efficacy of interventions designed to prevent low concentration of oxygen in brain tissue.

Cortical spreading depression in acute traumatic brain injury (COSBID)

A new multi-center trial being conducted at The Miami Project/UM is to evaluate whether the occurrence or severity of a secondary injury phenomenon called spreading depression is related to worse neurologic recovery following TBI. Spreading depression is a process of short-circuits in brain function, which arise spontaneously from an injury. These "short-circuits" spread repeatedly as waves into neighboring brain tissue and have been shown to cause secondary damage in animal studies. It is known that spreading depression occurs in a large proportion of

people with acute TBI during the first week post-injury. The information gained from this study will help neurosurgeons determine whether monitoring of spreading depression is a useful guide for medical management of TBI or is a target for therapeutic intervention.


NNZ-2566 in acute traumatic brain injury (INTREPID)

Another study that Miami Project neurosurgeons are participating in is a trial to evaluate a neuroprotective drug for acute TBI called NNZ-2566. NNZ-2566 is a synthetic analog of a trophic factor called Insulin-like growth factor (IGF-1). This drug has multiple functions. It has been shown to reduce inflammation in injured brain tissue, reduce cell death, protect neurons, and inhibit non-convulsive seizures that occur in the acute, post-injury period. This is a multi-center, randomized, placebo-controlled trial designed to identify the best dose of the drug that reduces side effects and improves brain function.

Oxycyte for acute traumatic brain injury

This trial will test the safety and efficacy of "Oxycyte," a perfluorocarbon that improves brain oxygenation. Oxycyte is an oxygen transport enhancer, capable of carrying four times the normal amount of oxygen than a normal human red blood cell. By introducing Oxycyte to the brain or spinal cord after injury, the investigators hope this will increase the oxygen delivered to the injured tissue and reduce the amount of permanent damage to nerve tissue. The Oxycyte trial is currently enrolling subjects in Switzerland and Israel and is scheduled to begin enrolling subjects at UM by 2012.

SLV334 for acute traumatic brain injury

Miami Project neurosurgeons recently began enrolling participants in a Phase II clinical trial to test the safety and efficacy of SLV334 in people with moderate or severe traumatic brain injury (TBI). SLV334 is a drug that is thought to be neuroprotective by reducing blood vessel constriction and reducing edema (swelling) in the injured brain. The drug must be administered within 8 hours post-injury. This trial is evaluating the safety and efficacy of single and multiple doses of increasing concentration to determine the correct dose for the future pivotal Phase III trial. 

Pre-clinical studies and clinical trials currently being conducted for acute or chronic spinal cord injury.

TREATMENT	POPULATION	PRE-CLINICAL	PHASES		
			1	2	3
AUTOLOGUS SCHWANN CELL	Acute & Chronic SCI	Ongoing			
BIO MARKERS OF SCI	Acute SCI		Pending		
NACTN	Acute SCI		Enrolling		
PREGABALIN	Chronic SCI				Enrolling
RILUZOLE	Acute SCI		IRB approval obtained		
ROLIPRAM	Acute SCI	Ongoing			
THERAPEUTIC HYPOTHERMIA	Acute TBI & SCI			Pending	

Ongoing clinical trials involving traumatic brain injury being run by Miami Project faculty members.

TREATMENT	POPULATION	PHASES	
		1	2
BIOMARKERS OF TBI	Acute TBI	Enrolling	
BOOST	Severe TBI		Enrolling
COSBID	Acute TBI	Enrolling	
INTREPID	Acute, Moderate, or Severe TBI		Enrolling
OXYCYTE	Acute, Severe TBI		Enrolling overseas
SLV 334	Acute, Moderate & Severe TBI		Enrolling
THERAPEUTIC HYPOTHERMIA	Acute TBI & SCI		Pending




Whole-body vibration is effective at reducing leg muscle spasms in some persons with chronic spinal cord injury

Recent findings from the laboratory of Dr. Edelle Field-Fote, a faculty member of The Miami Project to Cure Paralysis at the University of Miami, Miller School of Medicine demonstrate that whole-body vibration (WBV) may be an effective therapeutic intervention for reducing leg muscle spasticity in a sub-population of people living with a chronic spinal cord injury (SCI). In a recently published peer-reviewed research article in the journal *Restorative Neurology and Neuroscience* (2009, 27: 621–631), Dr. Field-Fote and members of her lab tested the effect of whole-body vibration therapy administered 3 days a week for a total of 12 sessions in individuals with a motor incomplete SCI who were experiencing chronic spasticity in the quadriceps muscle of the legs. One session consists of four, 45-second bouts of vibration with

one minute of seated rest (without vibration) between bouts. This is a protocol that her laboratory has used previously in persons with incomplete SCI and which was demonstrated to increase walking speed in those individuals (Ness and Field, 2009, *Gait & Posture* 30:436-440). In this newly published study, they observed a significant reduction in spasticity in the quadriceps muscle 15 minutes after participation in a single WBV session. Furthermore, they found that the reduction in leg muscle spasticity *persisted* for at least eight days after the 12 session therapy.

How does this work? Vibration is known to trigger both excitatory and inhibitory influences on spinal reflex circuitry, resulting in a phenomenon called “the vibration paradox.” Excitatory and inhibitory influences

cause the vibrated muscles to contract and relax. It is possible that the vibration-induced excitatory influences continue for a short time after each session of WBV, resulting in a temporary *increase* in spasticity, which was observed when tested immediately following a WBV session. Similarly, vibration-induced inhibitory influences may have a delayed onset that results in a *delayed reduction* in spasticity (which was observed when tested 15 minutes after a WBV session). Dr. Field-Fote’s data suggests that there is a progressive decrease in spasticity each week of the WBV intervention. It is thought that the long-term persistence of those inhibitory influences may be responsible for the overall spasticity-reducing effects of the WBV observed for 8 days following the 12-week intervention period.

What does this mean? It is known that in individuals with motor incomplete SCI who are able to walk to some degree, that spasticity can have a negative influence on their walking performance and subsequently impair the functional use of their walking ability. Dr. Field-Fote’s new results suggest that for individuals with SCI in whom spasticity interferes with their function or mobility, whole body vibration may be a useful therapeutic intervention. Additionally, whole body vibration may be a valuable adjunct to locomotor training interventions. Future studies need to 1) include a comparison group to determine if intervention parameters other than WBV may be responsible for the observed effect, 2) test different time intervals following WBV interventions to better characterize the persistence of the effects on reducing spasticity beyond the 8 days examined in the current study, and 3) evaluate the effectiveness of combining whole body vibration with locomotor training. 

Multi-disciplinary SCI pain research by Miami Project scientists




It may be difficult to comprehend that people who lack sensation may still experience pain, but there lies one of the many complexities of spinal cord injury (SCI). It is estimated that up to 70% of people with SCI develop chronic pain. There are many types of pain, but neuropathic pain is particularly resistant to treatment. Neuropathic pain results from damage to nerves, the spinal cord, or the brain. This causes imbalance and some nerve cells may become “overactive” and start sending incorrect signals that result in pain. These pain signals may be generated spontaneously, which means they are not necessarily provoked or triggered by activity in pain receptors. The neuropathic pain is resistant to treatment because: 1) the biologic mechanisms in the spinal cord and brain that underlie neuropathic pain development and persistence are not completely known; 2) people with SCIs usually have several different pain problems with different mechanisms; 3) we are not yet able to fully identify underlying mechanisms in a person with pain; and 4) pain is a multi-dimensional problem that involves many important psychosocial factors that need to be considered in both research studies and clinical practice.

The Miami Project has a multi-disciplinary group of scientists that are all doing research to understand and better treat neuropathic pain. Dr. Jacqueline Sagen performs basic science research to determine the biologic mechanisms contributing to chronic pain. She uses cell culture techniques as well as cell transplantation and animal models. In 2009 her laboratory demonstrated that a drug that stimulated the cannabinoid receptor was effective at reducing pain responses to mechanical stimulation and the animals that received the drug did not develop tolerance to it, a common problem with current drugs prescribed for humans. Additionally, she demonstrated that acetaminophen, which acts in part by inhibiting the degradation of naturally occurring cannabinoids in the body, in combination with morphine or gabapentin has a greater effectiveness (synergistic) on reducing pain than either drug alone. Her lab also discovered that 2 types of small

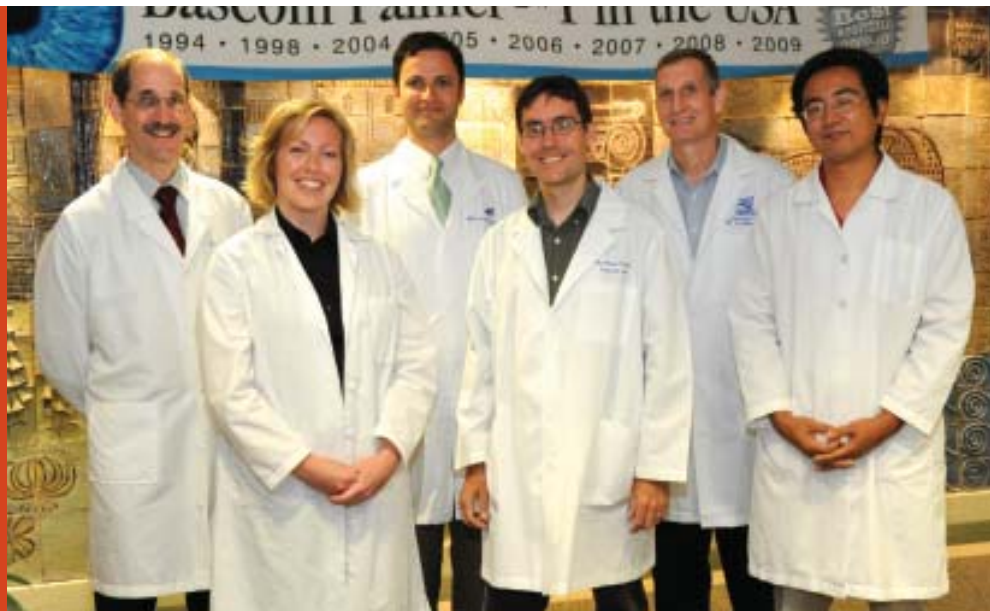
proteins (peptides) derived from the marine cone snail were very effective, especially when given in combination, at reducing pain responses in spinal injured animals. These identified promising targets are being utilized in the generation of engineered cells and gene therapy vectors to produce sustained delivery of analgesic peptides for long-term pain alleviation.

Dr. Diana Cardenas focuses her research on the opposite end of the spectrum. She is a Physical Medicine and Rehabilitation clinician so she treats people with SCI on a daily basis and her research focuses in the biopsychosocial realm. In 2009 her research team identified psychological factors that impact pain outcome. In particular, they determined that perception of oneself as disabled, perceptions of low control over pain, and tendency to catastrophize were predictors of negative pain outcome. Another study demonstrated that self-hypnosis training was more effective than biofeedback relaxation training on reducing pain intensity and average daily pain. This effect persisted for at least 3 months after the 10 session program.

Dr. Eva Widerström-Noga conducts clinical science research focused on methods to quantitatively describe and measure neuropathic pain experienced by people living with SCI. In 2009 she and her colleagues demonstrated that Quantitative Sensory Testing (measurement of pain responses to vibratory, mechanical, and temperature stimuli) is a valid and reliable measure of quantifying the neurologic dysfunction associated with neuropathic pain. Other studies characterized pain symptoms profiles, determined that pain-interference with daily functions is a pain measure that is highly sensitive to change and therefore an important outcome measure, and that how well a person adapts to pain is not only dependent on personal ability but also on the type of pain experienced, in that neuropathic pain is more difficult to adapt to than other pain types. Her laboratory is utilizing all of these results to identify pain phenotypes, i.e., patterns of pain symptoms and signs, in order to link these to underlying mechanisms of pain and to aid in the development of treatments that target these mechanisms.

In sum, The Miami Project is committed to conducting research and developing therapies for all the dysfunctions caused by SCI. Our pain researchers are just one example of our ability to perform research utilizing multiple approaches and disciplines to better understand and treat complications that are important to the community living with SCI. 

Researchers Identify Protein Family Responsible for Regulating Nerve Regeneration



Drs. Vance Lemmon, Darcie L. Moore, Jeffrey Goldberg, Murray Blackmore, John Bixby and Ying Hu

The ability to reconnect nerve cells is essential to being able to restore function in individuals suffering from conditions and diseases such as spinal cord injury, traumatic brain injury, glaucoma, stroke, and other neurodegenerative diseases of the brain and spinal cord.

Researchers at the University of Miami Miller School of Medicine have identified a family of proteins that may control the ability of nerve cells to reconnect to each other. The discovery of this protein family, as published in the October 9, 2009, issue of *Science*, is a big step forward for research involving regeneration of the nervous system. The ability to reconnect nerve cells is essential to being able to restore function in individuals suffering from conditions and diseases such as spinal cord injury, traumatic brain injury, glaucoma, stroke, and other neurodegenerative diseases of the brain and spinal cord.

All nerve cells have long thread-like processes, called axons, which send electrical impulses from one nerve cell to the next, much like a telephone wire. If the axons of nerve cells in the brain or spinal cord are damaged because of injury or disease, these electrical signals are not able to reach their targets. Without proper electrical communication between nerve cells and muscles (or other organs), paralysis and loss of feeling can occur. It has been known for many years that nerve cells in the adult brain and spinal cord have a very poor ability to reconnect, i.e., the cut or damaged axons cannot grow back to their targets.

A team of scientists from the University of Miami's The Miami Project to Cure Paralysis and Bascom Palmer Eye Institute have worked together to study this problem. Jeffrey Goldberg, M.D., Ph.D., Assistant Professor of Ophthalmology, explained that nerve cells in the brain and spinal cord grow normally during fetal development and childhood, but turn off their growth ability as adults. It is normal, and necessary, for that growth ability to be turned off when it is completed. As a consequence, however, nerve cells cannot reconnect properly when they are injured in adults. The optic (eye) nerve is a common tissue used by scientists to study why axon growth failure occurs in damaged, adult nerve cells.

Members of the **Vance Lemmon-John Bixby (LemBix)** lab in The Miami Project have devoted the last several years to developing laboratory methods for testing hundreds of proteins simultaneously for their ability to increase or decrease axon growth. They use automated microscopes to visualize and measure the changes in nerve cells growing in a cell culture dish. Dr. Goldberg's Ph.D. student, Darcie L. Moore, used this approach to test more than 100 proteins in an effort to identify which would be involved in the growth of optic nerve axons. She discovered that



Drs. Darcie L. Moore and Murray Blackmore; Neurons growing long axons in culture

one protein, Krüppel-like factor-4 (KLF4), prevents growth of optic nerve axons as well as axons from other brain and spinal cord nerve cells. KLF4 is produced at very low

levels early during development and then turned off when axon growth was completed—the opposite of KLF6. These studies showed that KLF6, needs to be present, and KLF4


like KLF4, while others stimulate axon growth (positive), like KLF6. Importantly, when they tested the ability of different combinations of positive and negative KLFs to work

This finding could be important for designing treatments that use the different KLF genes to stimulate axon growth in the damaged spinal cord and brain. This should permit them to send electrical signals once again to their targets, in an effort to restore lost function.

levels in the developing brain and in higher quantities in the adult brain. Amazingly, **Dr. Murray Blackmore**, a postdoctoral fellow in the LemBix lab at the time, found a protein related to KLF4, called KLF6, in a similar test using nerve cells from the brain. He was studying proteins that were turned on or turned off during development in nerve cells that send their axons down to the spinal cord. He discovered that KLF6 was produced at higher

absent, when damaged nerve cells are trying to regrow their axons and reconnect with their targets.

The research team expanded their studies to test the whole KLF family, which includes 17 members, and found that the entire family of proteins may play important roles in controlling the ability of damaged nerve cells to reconnect to one another. Some KLFs prevent axon growth (negative),

together, they found that the negative KLFs can prevent the positive KLFs from stimulating axon growth. This finding could be important for designing treatments that use the different KLF genes to stimulate axon growth in the damaged spinal cord and brain. This should permit them to send electrical signals once again to their targets, in an effort to restore lost function. 

Are there similarities between Spinal Cord Injury and Multiple Sclerosis?




Roberta Brambilla, Ph.D. working in the Bethea Lab

The question becomes, why would our own immune system cause additional injury to the spinal cord following trauma, or, in the case of MS, why would our own immune system attack seemingly healthy nervous tissue resulting in paralysis?

Some people may ask what do spinal cord injury (SCI) and multiple sclerosis (MS) have in common? Why would a scientist at The Miami Project to Cure Paralysis, the foremost SCI research center in the world, study an autoimmune disease? In fact, there are many similarities between SCI and MS and the knowledge we gain is important in our endeavor to develop effective treatments to restore function to people living with paralysis. MS is the leading cause of non-trauma induced paralysis and, like SCI, people suffering from MS have severe nerve cell damage, myelin loss, and often times suffer with severe pain and loss of bladder control. Another important similarity between these two debilitating neurological disorders is that it is believed that our own immune system is responsible for causing much of the damage. Dr. John Bethea and his research team are interested in better understanding how our own immune system attacks healthy nerve tissue, following trauma-induced SCI or non-trauma-induced MS, and how this results in neurological damage and paralysis.

We all recognize the importance of an immune response in fighting infections that may occur during an illness or after an injury. In fact, if our immune system was not functioning properly the simplest wound or injury would never heal and, as you can imagine, would cause even more problems. The question becomes, why would our own immune system cause additional injury to the spinal cord following trauma, or, in the case of MS, why would our own immune system attack seemingly healthy nervous tissue resulting in paralysis?

We do not yet fully understand why these immune responses occur, but recent studies from Dr. Bethea's lab have shown that inhibiting a key protein important in regulating immunological responses in a cell found exclusively in the brain and spinal cord significantly reduces the paralysis associated with mouse models of SCI and MS. The cell type in question is an astrocyte, the most abundant cell in the central nervous system (CNS). Astrocytes are a type of glial cell and can be considered very important support cells for the CNS. The research team has also shown that when this key regulatory protein is inhibited in astrocytes, the immune response that would normally be triggered in these mouse models of SCI and MS is greatly diminished, which results in reduced neuronal cell death.

From these studies, Dr. Bethea and his team have identified several new targets that they are testing as potential therapies for SCI and MS. One example using a mouse model of MS has shown that inhibiting two different immune-signaling proteins after the animals are already paralyzed improves their neurological function extensively. Studies are underway to optimize these therapies and to test them in a model of SCI. 

The Miami Project is proud to welcome Kim Anderson-Erisman, Ph.D., as our new Director of Education

Prior to joining our team, Dr. Anderson-Erisman was an Assistant Professor in the Department of Neurological Surgery at the University of California, Irvine and a core faculty member of the Reeve-Irvine Research Center. Her previous research has focused on translational investigations and bridging the gap between basic science, clinical science, and the public community living with spinal cord injury (SCI). Her training spans the spectrum of SCI research, from cellular and molecular studies as a graduate student, to whole animal and behavioral studies as a post-doctoral fellow, to human clinical research as a faculty member. This breadth of knowledge will be a great attribute in her new role as the

scientific interface to the public for the diverse array of cutting-edge research being conducted at The Miami Project.



A special perspective that Dr. Anderson-Erisman brings to the SCI research field is that she also has a spinal cord injury. When she was seventeen years old she was involved in a motor vehicle accident that left her with quadriplegic paralysis from a cervical spinal cord injury. After graduating from high school without delay, she went on to college at Texas A&M University and graduate school at the University of New Mexico. She has received numerous awards, including the Khatali Award

for Outstanding Senior Graduate Student, a NIH National Research Service Award as a post-doctoral fellow, the Paul H. Silverman Award for Outstanding Work on Science and Ethics in 2005, and was inducted into the SCI Hall of Fame in 2007. She is a member of many professional organizations, serves on the NIH National Advisory Board for Medical Rehabilitation Research, and serves on the Pan-Canadian Spinal Cord Injury Solutions Network-Translational Research Program Research Advisory Committee. In 2008 she completed a comprehensive certification program for *Clinical Trials: Medical Device and Drug Development*. By using her training in clinical trial regulations and extensive connections within the SCI clinical community, Dr. Anderson-Erisman will be directly involved in developing the clinical trial involving Schwann cells that The Miami Project is pursuing.

Gail F. Beach Memorial Lecture Series

The Miami Project has brought many renowned neuroscientists from around the world to our campus as part of The Gail F. Beach Memorial Visiting Lectureship Series. The lectureship series is dedicated to Gail F. Beach, a schoolteacher and person with SCI, whose generosity and foresight provides outstanding educational opportunities for The Miami Project researchers and our neuroscience colleagues at the University of Miami.

December 2, 2009

Eberhard E. Fetz, Ph.D.

Washington National Primate Research Center
University of Washington, Seattle

"Applications of Recurrent Brain-Computer Interface"

February 3, 2010

Gordon Fishell, Ph.D.

Smilow Neuroscience Program
New York University School of Medicine

"Making Up Your Mind: The Origins and Integration of Cortical Interneurons into Brain Circuitry"

March 3, 2010

Steve A. Goldman, M.D., Ph.D.

School of Medicine and Dentistry
University of Rochester

"Progenitor Cell-based Strategies for Treating Diseases of the CNS"

April 7, 2010

Oswald Steward, Ph.D.

Reeve-Irvine Research Center
University of California, Irvine

"Promoting Axon Regeneration in the Injured Spinal Cord"

May 5, 2010

John A. Kessler, M.D.

Center for Genetic Medicine
Northwestern University Institute of Neuroscience

"Regulation of Glial Scar Formation after Spinal Cord Injury"

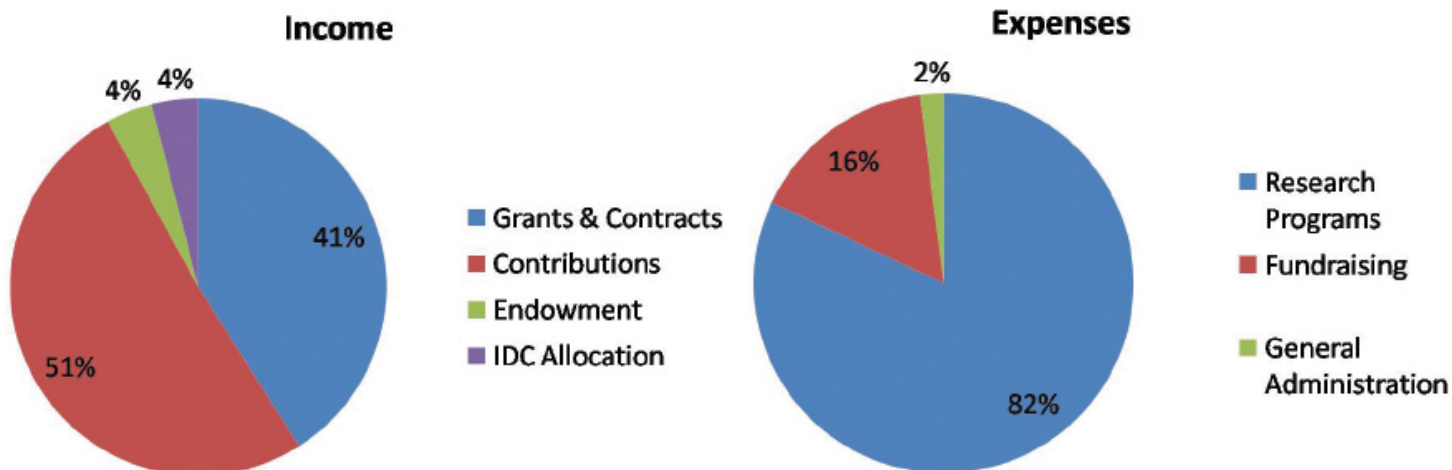
June 2, 2010

Alvaro Pascual-Leone, M.D., Ph.D.

Beth Israel Deaconess Medical Center
Harvard Medical School

Each year, Miami Project scientists seek funding for their research by submitting proposals to the National Institutes of Health, the premier scientific body in the United States, as well as other funding agencies and foundations.

Their scientific peers rate the merits of these proposed experiments in a highly competitive process and only the best are funded. The agencies and organizations listed below supported the Principal Investigator(s) and the scientific project(s) indicated during fiscal year 2008-2009.



Department of Defense Congressionally Directed Medical Research Programs

Dr. M. Ross Bullock

-Phase IIB Trial of the Perfluorocarbon Oxycyte in Severe Human Head Injury

-Treatment of Traumatic Brain Injury Using the Neuroprotectant NNZ2566

-Spreading Depressions as Secondary Insults after Traumatic Injury to the Human Brain

National Institute of Neurological Disorders & Stroke

Dr. W. Dalton Dietrich

-Cyclic Nucleotide Regulation in Traumatic Brain Injury

Dr. W. Dalton Dietrich

Dr. John Bixby

Dr. Damien Pearse

-Training Program in CNS Injury and Repair

Dr. Jacqueline Sagen

-Neural Transplants and Spinal Neuropathic Pain Processes

-Translational Model for Novel Therapeutics in Spinal Cord Injury Pain

Dr. John Bethea

-The Role of Astroglial-NF- κ B in SCI

-Astrocytes Play a Critical Role in the Pathology of EAE

Dr. Damien Pearse

Dr. Mary Bartlett Bunge

Dr. Brian Noga

Dr. Patrick Wood

-Axon Regeneration: Synergistic Actions of the MAPK and Cyclic AMP Pathways

Dr. Allan Levi

-Transplantation of Autologous Schwann Cells for the Repair of Segmental Peripheral Nerve Defects

Dr. Daniel Liebl

-Ephrins Regulate Stem Cell Proliferation Following Traumatic Brain Injury

Dr. Mary Bartlett Bunge

Dr. Paula Monje

Dr. Patrick Wood

-Cytological Studies of Developing and Mature Neurons

Dr. Brian Noga

-Control of Spinal Locomotor Activity by Monoamines

Dr. W. Dalton Dietrich

Dr. Helen Bramlett

-The Importance of Temperature on Inflammation after TBI

Dr. Christine Thomas

-Muscle Function in Human Cervical Spinal Cord Injury

Dr. John L. Bixby

Dr. Vance P. Lemmon

-Novel Compounds That Overcome Glial Inhibition of Axonal Regeneration

National Institute on Disability and Rehabilitation Research

Dr. Edelle Field-Fote

Dr. Mark S. Nash

-RRTC on Prevention of Secondary Conditions through Exercise: A Participatory Approach for People with Spinal Cord Injury

Dr. Mark S. Nash

-Exercise Interventions for Spinal Cord Injured Adults with Obesity-Related Secondary Disorders

National Institute of Child Health & Human Development

Dr. Edelle Field-Fote

Dr. Diana Cardenas

Dr. Mark S. Nash

-Improving Hand and Arm Function in Individuals with SCI

Dr. Edelle Field-Fote

-Adaptive Control of Flexion Withdrawal Reflex Stimulator for Locomotor Rehabilitation

Dr. Vance Lemmon

Dr. John Bixby

--Novel Gene Targets for CNS Axonal Regeneration

U S Army Medical Research & Material Command

Dr. W. Dalton Dietrich
 Dr. John Bethea
 Dr. John Bixby
 Dr. Vance Lemmon
 Dr. Daniel Liebl
 Dr. Damien Pearce
-Battlefield Exercise and Combat Related Spinal Cord Injury
 Dr. W. Dalton Dietrich
 Dr. Helen Bramlett
-The Use of Lentiviral-Vector-Mediated Transduction of Neural Progenitor Cells to Repair the Brain after Traumatic Brain Injury
 Dr. Helen Bramlett
-Pathophysiology of Polytrauma and Novel Treatment Strategies
 Dr. Ian Hentall
 Dr. Helen Bramlett
-Electrical Stimulation of the Midbrain to Promote Recovery from Traumatic Forebrain Injury

Veteran Affairs Medical Center – Miami

Dr. W. Dalton Dietrich
-Interagency Personnel Agreements – Ofelia Furones-Alonso
 Dr. W. Dalton Dietrich
-Interagency Personnel Agreements – Helen M. Bramlett
 Dr. Eva Widerstrom-Noga
-Interagency Personnel Agreements – Jim Adcock
 Dr. Eva Widerström-Noga
 Dr. Diana Cardenas
 Dr. Alberto Martinez-Arizala
-Magnetic Resonance Spectroscopy as a Diagnostic and Outcome Measure in Clinical Pain Trials Involving People with Spinal Cord Injury

Florida State Department of Health

Dr. W. Dalton Dietrich
- Brain and Spinal Cord Injury Rehabilitation Trust Fund

Bryon Riesch Paralysis Foundation**Hearst Foundation, Inc.**

Dr. Damien Pearce
-Examination of the Toxicology Profile and Neuroprotective Efficacy of the PDE Inhibitors in Non-Human Primates after SCI

Craig H. Neilsen Foundation

Dr. John Bethea
-The Role of Astroglial-NF- kappa B in Regenerative Sprouting and Neuroprotection
-The Role of NF-kappaB in Neuronal Growth and Differentiation
 Dr. Ian Hentall
 Dr. Damien Pearce
-Chronic Brainstem Stimulation to Improve Recovery after Spinal Cord Injury
 Dr. Mark S. Nash
-Effects of Exercise on Prandial Lipemia and Fat Oxidation after Tetraplegia
-Effects of Salsalate Monotherapy on Prandial-Induced Vascular Inflammation in Overweight Persons with SCI
 Dr. Damien Pearce
 Dr. Mousumi Ghosh – Fellowship
-Repair of Spinal Cord Injury by Surface Modified Schwann Cells
 Dr. Jaqueline Sagen
-Identification and Rapid Screening of Novel Treatments for SCI Pain
 Dr. Vance Lemmon
-Identification of Corticospinal Track Regeneration-Associated Genes

Dr. Christine Thomas

-Automatic Analysis of Spasms in Human Muscles Paralyzed by Spinal Injury

Christopher & Dana Reeve Foundation

Dr. Mary Bartlett Bunge
 Dr. Damien Pearce
-Research Consortium on Spinal Cord Injury
 Dr. James Guest
-North American Clinical Trials Network

Memorial Sloan-Kettering Cancer Center

Dr. Damien Pearce
-Use of Polysialic Acid in Repair of SCI

McKnight Brain Research Foundation – University of Florida

Dr. Mary Bartlett Bunge
-Transplantation of Adult Neural Progenitors (AHNPS) into the Contused Adult Rat Spinal Cord

Paralysis Project of America

Dr. Damien Pearce
-Rolipram and Hypothermia for Cervical Spinal Cord Injury Repair

Ironwood Pharmaceuticals, Inc.

Dr. Jacqueline Sagen
-Testing Analgesic Effects of FAAH Inhibitors in a Rat Spinal Cord Injury Pain Model

National Football League Charities

Dr. Allan Levi
-Therapeutic Hypothermia Following Severe Spinal Cord Injury

PVA Education Foundation

Dr. Rachel Cowan
-From Research into the Clinic: The Manual Wheelchair Propulsion Database

Ralph C. Wilson Jr. Medical Research Foundation

Dr. Mary Bartlett Bunge
 Dr. Patrick Wood
-Development of Improved Conduits to Introduce Cells, Growth Factors and Extracellular Matrices into the Injured Rat Spinal Cord
 Dr. Vance Lemmon
-Identification and Testing of Corticospinal Track Regeneration-associated Genes
 Dr. Jacqueline Sagen
-Cell and Gene Therapy Strategies for Delivery of Novel Marine Snail Peptides in Chronic Spinal Cord Injury Pain

Shriners Hospital For Children

Dr. W. Dalton Dietrich
-Recovery From Injury in Newborn but Not Older Opossums: Gene Regulation And Protein Expression

San-Bio Pharmaceuticals

Dr. Jaqueline Sagen
-Effects of SB 623 Cell Implantation in Spinal Cord Injured Rats

The Wallace H. Coulter Center for Translational Research at the University of Miami

(Intramural)
 Dr. John L. Bixby
-RPTPs in the Growth of Vertebrate Axons



The Miami Project's research faculty is a talented multidisciplinary team. In the following Faculty Profiles, each team member describes their specific research focus and recent progress.

Barth A. Green, M.D., F.A.C.S.

Co-Founder and Chairman, The Miami Project To Cure Paralysis

Professor and Chairman, Department of Neurological Surgery

Professor, Departments of Orthopedics and Rehabilitation Medicine

Laboratory Focus: Translational investigations for the treatment of neurotraumatic injuries

Laboratory Summary: My major area of research at The Miami Project involves translational investigations in the use of modest hypothermia for treatment and neuroprotection in acute spinal cord injury as well as acute brain injury or other neurotrauma injuries. Each of these clinical investigations is in collaboration with both basic scientists and clinical researchers at The Miami Project to Cure Paralysis and the Department of Neurological Surgery and our collaborating medical school departments. The results of clinical studies have been published demonstrating the safety of using modest hypothermia in acute spinal cord injured patients and, most recently, demonstrating measurable improvements in neurological function. A more comprehensive prospective, multi-center study to quantitate the effectiveness of modest hypothermia as a neuroprotective agent in acute spinal cord injury has been designed and is being reviewed in the National Institutes of Health by the Neurological Emergencies Treatment Trials (NETT) group. In that study I will be a co-investigator with my neurosurgical colleague Dr. Michael Wang being the national principle investigator. I am also an active participant in The Miami Project translational program directed at the use of human autologous Schwann cells as a cellular therapy in both acute and chronic spinal cord injury. This again is in collaboration with The Miami Project basic science and clinical research teams as well as many other departments and programs at The University of Miami Miller School of Medicine. This is an extraordinary effort that involves a multitude of scientists, technicians, and clinicians focused on using cellular therapy as a treatment for both acute and chronic spinal cord injury.



In addition, I am a very active collaborator with research programs primarily directed by the departments of Radiology, Genetics, Neurology, and other members of our neuroscientific university community. At this point in my career I am totally committed to being a team member rather than leader and principle investigator and I work as both a mentor and a student in a very special position and environment, which is an opportunity that few of my colleagues around the world have enjoyed. Through The Miami Project's exceptional scientists and well-organized initiatives, we collectively have been able to affect the practice of medicine in many different arenas and have contributed techniques and technology which are being used by physicians not only in the United States, but around the world. These contributions and my participation in The Miami Project program represents the most satisfying part of my forty-year career as a physician and my thirty five-year tenure as a faculty member, now among the leadership at The University of Miami Miller School of Medicine.



W. Dalton Dietrich, Ph.D.

Scientific Director and Professor, Neurological Surgery, Neurology, and Cell Biology & Anatomy

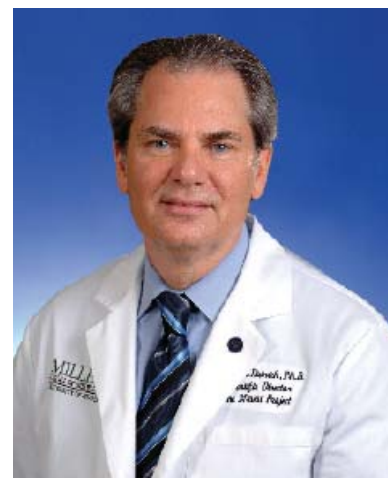
Laboratory Focus: Neuroprotection and Improved Recovery of Function following CNS Trauma

Laboratory Summary: The Brain and Spinal Cord Injury Laboratory continues to focus on the development of new strategies to protect and promote recovery after CNS injury. Our laboratory has developed clinically relevant neurotrauma models to investigate molecular mechanisms of cell death and novel treatments including cellular therapies to promote functional recovery. We are most interested in the translation of our discoveries to the clinic. This year, several projects have yielded important results.

Recent studies have demonstrated the neuroprotective effects of controlled hypothermia following traumatic brain injury (TBI). Brain cooling has been shown to protect the brain histopathologically and to improve functional outcome. We recently demonstrated that hypothermia administered after TBI reduces the trauma-induced permeability of the blood brain barrier. This year we also completed a single center clinical study demonstrating that administration of modest hypothermia early after spinal cord injury is feasible, safe, and potentially beneficial.

Bone morphogenetic protein 7 (BMP7) has been shown to enhance functional recovery after neural injury. BMP7 expression is modulated by SCI, but the molecular mechanisms involved in neuroprotection have not been clearly defined. We demonstrated that BMP7 treatment of rats subjected to mild cervical SCI significantly increased pro-survival signaling pathways, which resulted in a significant increase in neuronal sparing in the ventral horn of the spinal cord. Additionally, BMP7 was neuroprotective against glutamate-mediated excitotoxicity in cultured cortical neurons. These studies show that BMP7 administration may be used as a neuroprotective therapeutic strategy to reduce the damaging excitotoxic effects following SCI.

Notable accomplishments: Dr. Dietrich was invited to speak about his research at several scientific meetings during 2009, including the Critical Care Congress, the American Society of Spine Radiology, the International Consensus Conference in Intensive Care Medicine, the International Hypothermia Symposium, the National and International Neurotrauma Symposium, the Howard Steel Conference, and the International Symposium on Neural Regeneration. He also served on several grant review panels, including the Craig H. Neilsen Foundation and the NIH.

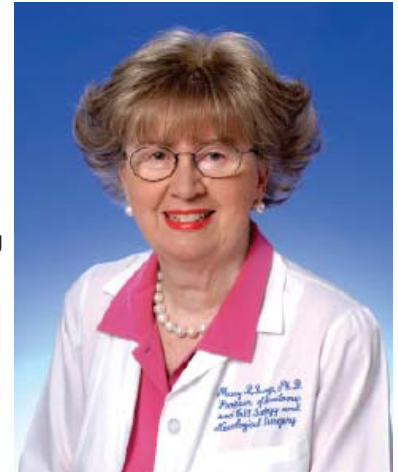


Mary Bartlett Bunge, Ph.D.

Christine E. Lynn Distinguished Professor in Neuroscience; Professor, Cell Biology & Anatomy, Neurological Surgery and Neurology

Laboratory Focus: Development of Combination Strategies to Repair the Injured Spinal Cord

Laboratory Summary: The goal in my laboratory is to foster regeneration of axons across and beyond a spinal cord injury (SCI). To improve regeneration of axons after SCI, we are investigating interference in the accumulation of proteoglycans (molecules that inhibit axonal growth), improved survival of transplanted Schwann cells, and genetic engineering of these cells before transplantation to improve their neurotrophic factor-secreting capability or of neurons to enhance their ability to regenerate axons after injury. We also have initiated a microarray study to detect gene differences between neurons that regrow axons into a cellular bridge placed in the area of injury and those that do not extend axons into the bridge.



Dr. Caitlin Hill is comparing differences in the mRNA and protein content of extending growth cones vs. retraction bulbs. If we understand the differences, we might then know how to treat retraction bulbs so they would transform into growing nerve fibers tipped by growth cones. She is also studying ways to improve Schwann cell survival and proliferation after transplantation. Ryan Williams, a Ph.D. student, unexpectedly discovered that brainstem axons can regenerate into a Schwann cell bridge without additional interventions if the SC/bridge material is placed in the injury site before solidifying. Dr. Chikato Mannoji, in a collaboration with the University of Florida, is evaluating the differentiation of adult neural precursor cells when transplanted into our complete transection injury paradigm. He also is evaluating the effect of transplanting these cells in combination with nanofiber scaffolds and Schwann cells.

Notable accomplishments: Dr. Bunge continues to serve on the Public Education and Communication Committee for the Society for Neuroscience. She has recently completed 15 years as a member of the Christopher and Dana Reeve Foundation International Research Consortium.

M. Ross Bullock, M.D., Ph.D.

Professor, Neurological Surgery; Director, Clinical Neurotrauma

Laboratory Focus: Preclinical Mechanistic and Neuroprotection Research in Traumatic Brain Injury and Clinical trials, and Neuromonitoring Techniques in the Injured Brain

Laboratory Summary: Many mechanisms of injury as well as strategies for neuroprotection and repair are common to both severe traumatic brain injury (TBI) and spinal cord injury (SCI). An important focus in my laboratory is the possibility of promoting repair by augmenting endogenous progenitor cells or by using cell transplantation strategies. We are currently working on modulating neurogenesis and thus improving cognitive recovery after neurotrauma. This work eventually offers the prospect of enhancing recovery in people with residual severe neurological deficit after TBI. We are very much interested in another project in which we are isolating and culturing neural progenitor cells from people with acute brain damage, then transplanting them into rats with TBI. Preliminary results demonstrate increased proliferation of the grafted cells and robust incorporation into the hippocampus. Anna Delarolle, Ph.D., with 5 years experience in endogenous neurogenesis, will direct this aspect.



New drug therapies also offer the possibility of ameliorating the neuronal death that occurs in TBI. We are particularly excited about two projects. The first of these is a study to examine the use of Oxycyte™ in animal models of spinal cord injury. Our pilot data has shown promising results and thus may have important implications for functional recovery. Dr. Amanpreet Singh, senior Assistant Scientist in our lab, is the project manager for this study. A second project is to study the role of Oxycyte™ on tissue preservation after transient focal ischemia in rats. This project has been successfully started by Dr. Amade Bregy, a postdoctoral candidate.

Notable Accomplishments: Dr. Bullock was appointed as the Chair of the Department of Defense Congressionally mandated Advisory Board for Traumatic Brain Injury and is President-elect of the National Neurotrauma Society.

**John Bixby, Ph.D.; Professor, Departments of Pharmacology and Neurological Surgery;
Associate Dean for Graduate Studies**
**Vance Lemmon, Ph.D.; Walter G. Ross Distinguished Chair in Developmental Neuroscience;
Professor, Neurological Surgery**
Laboratory Focus: High Content Screening and Functional Genomics of the Nervous System

Laboratory Summary: The mass of information available from the various genome projects, together with sophisticated image analysis and laboratory automation has created an opportunity to revolutionize the study of the nervous system. Our laboratory has developed methods to test hundreds of genes in hundreds of thousands of neurons each week and obtain quantitative information about cell morphology and gene expression. This “high throughput” capability allows us to tackle questions about development and regeneration using Systems Biology approaches. The biological problem we have focused on for the past six years has been to uncover genes that promote or prevent axon regeneration.

The Lemmon-Bixby lab has four ongoing projects related to axon regeneration. The first project springs from the fact that neurons in the peripheral nervous system are able to regenerate while neurons in the central nervous system (CNS) are not. By analyzing data from several molecular biological approaches we were able to identify 900 genes that are preferentially expressed in regenerating peripheral neurons; of particular interest is a sub-list of 40 transcription factors (TFs) that are likely to regulate expression of other genes. The top TF has been confirmed to enhance neurite growth when over-expressed in CNS neurons.

Our second project is based on the fact that young CNS neurons have a greater regenerative capacity than old CNS neurons (collaboration with Dr. Jeff Goldberg). We have used DNA microarray data to generate a list of 800 candidate genes. We have tested about 60% of the genes on our list, and have identified 4 TFs that have a robust effect on neurite growth: two enhance growth and two inhibit growth. Interestingly, the two TFs that enhance growth show decreased expression as development proceeds, and the two that inhibit axon growth show increased expression as the animal ages. The results of this project were recently published in *Science*, the world’s leading journal of original scientific research (Moore, D., M. Blackmore, Y. Hu, K.H. Kaestner, J.L. Bixby, V.P. Lemmon, and J.L. Goldberg, KLF family members regulate intrinsic axon regeneration ability. *Science* (2009) 326:298-301 PMID: 19815778).

The third project is to test effects of overexpression of known signaling proteins (kinases and phosphatases). In this screen we have tested 724 genes, and have found a high percentage with significant effects on neurite growth (about 40 total). The data from this screen is allowing us to begin to build models of neuronal signaling networks underlying axon regeneration. We are also using cheminformatics (collaboration with Stephan Schuerer) to identify chemicals that alter the activity of the interesting signaling molecules.

The fourth project is to screen a chemical compound library to identify compounds that can overcome the regeneration-inhibitory effects of the injured CNS (collaboration with Prof. Young-Tae Chang, National University of Singapore). We have identified four compounds that enhance axon growth of a variety of neurons in inhibitory environments. One of these has been found to enhance regeneration in an acute spinal cord injury model in vivo.

Notable accomplishments: Dr. Lemmon was an invited speaker on “Regeneration and Plasticity of Neural Circuits” at the *Cambridge Centre for Brain Repair Spring School* in Cambridge, England. Dr. Lemmon also joined the Center for Computational Sciences (CCS) at the University of Miami. Dr. Bixby served as a member of the Howard Hughes Medical Institute *Phase I Grant Review for Med-into-Grad Proposals* and has become a regular member of the NDPR (Neurodifferentiation, Plasticity, and Regeneration) grant review panel at the NIH. In the past 6 months, Dr. Lemmon was awarded a Grand Opportunities grant from the NIH for a collaborative project with the CCS, and Drs. Bixby and Lemmon were awarded a grant from the State of Florida for work on regeneration genes in animal models of spinal cord injury.



John Bixby, Ph.D.



Vance Lemmon, Ph.D.

Diana D. Cardenas, M.D., M.H.A.

Professor & Chair, Department of Rehabilitation Medicine, Chief of Service, Medical Director

Laboratory Focus: Pain Interventions and Prevention of Urinary Tract Infections

Laboratory Summary: The goals of my research are to help find therapeutic interventions that improve recovery, reduce secondary conditions, and create a better life for persons with SCI and other conditions that impair physical or cognitive function. Currently, I am working in the following areas:

1. Neuropathic pain: I have been collaborating with researchers from the University of Washington on pain studies for more than a decade to try to improve our medical management of pain. I conducted the first randomized clinical trial on the use of a tricyclic antidepressant, amitriptyline, for chronic pain in persons with SCI. In addition, our Seattle group surveyed hundreds of people with SCI and found that while many treatments are tried for pain in SCI, few are helpful. Many persons seek alternative medicine treatments which led us to study self-hypnosis. Since moving to Miami in 2006, I have been collaborating with Dr. Eva Widerström-Noga on studies of the underlying changes that may occur in the brain in persons with pain and SCI using Magnetic Resonance Spectroscopy. I am currently participating in another randomized clinical trial on the use of Lyrica, an anti-convulsant, for chronic pain in persons living with chronic SCI.

2. Neurogenic bladder management: I am currently completing a study to determine if hydrophilic catheters reduce the incidence of urinary tract infections (UTIs) in persons with SCI who manage their bladder with intermittent catheterization. This study involves 16 centers from the US and Canada. Despite the improvements made in the area of bladder management, many persons with SCI still have problems with recurrent UTIs.



Edelle C. Field-Fote, Ph.D., P.T.

Professor, Departments of Physical Therapy and Neurological Surgery

Laboratory Focus: Motor Restoration after Spinal Cord Injury

Laboratory Summary: The studies in the Neuromotor Rehabilitation Research Laboratory cross the boundaries of basic neurophysiology of the brain and spinal cord and applied neurophysiology related to neuroplasticity and motor learning. We want to understand which interventions best promote recovery of function. Some of the rehabilitation studies focus on recovery of hand and arm function, while others are aimed at walking function.

Experiments in my lab have shown that the brain is altered by SCI, and these alterations contribute to deficits of hand function in individuals with tetraplegia. By using practice and stimulation to engage the brain, we have been able to improve functional use of the hands in individuals with tetraplegia who have minimal hand function. Further, these studies have also shown that there are changes in the brain that accompany and support these improvements in hand function. At the level of the spinal cord, there is evidence that neural circuits are much “smarter” than we had previously thought. Like the circuits in the brain, the circuits in the spinal cord also change in response to practice and in response to electrical stimulation. These changes represent an elementary form of learning. Studies in the Neuromotor Rehabilitation Research Laboratory capitalize on this learning to promote improved walking function.

While rehabilitation is not a “cure”, it offers restorative strategies that are available today, and which make use of the innate capacity of the brain and spinal cord to adapt in response to experience, practice, and sensory inputs. Ultimately, identifying optimal restorative strategies will be critical for the success of regenerative strategies as well, since regenerative strategies are likely to be optimally effective only when combined with effective rehabilitation.

Notable Accomplishments: Dr. Field-Fote is Editor-in-Chief of the *Journal of Neurologic Physical Therapy*.



Allan D. Levi, M.D., Ph.D.

Professor, Neurological Surgery, Orthopedics, and Rehabilitation; Chief of Neurospine Service, Jackson Memorial Hospital; Chief of Neurosurgery, University of Miami Hospital

Laboratory Focus: Cellular Transplantation Strategies after Spinal Cord Injury

Laboratory Summary: My research interests have focused on developing cellular transplantation strategies to repair injuries within both the human central and peripheral nervous system. Schwann cells are the principal support cells with the peripheral nervous system and have the capacity to promote regeneration of central nervous system neurons as well as remyelinate central axons which have lost their insulation. I have focused much of my previous research efforts in furthering our understanding of the biology of human Schwann cells which have been isolated using cell culture techniques. The results of these studies have demonstrated that human Schwann cells have the capacity to form myelin after transplantation within immune deficient rodent models and that their numbers can be significantly increased with addition of growth factors.



My current research interests involve (1) further studies on the human Schwann cells extensively expanded in cell culture to determine whether the functional capacity of these cells with respect to myelination and regeneration are retained when compared to primary Schwann cell cultures, and (2) the development and characterization of a model of a peripheral nerve injury with a lengthy gap in the rat so that we can further characterize the influence of transplanted Schwann cell grafts within a collagen based channel on peripheral nerve regeneration.

Notable Accomplishments: Dr. Levi was awarded an NIH grant to study *Transplantation of autologous Schwann cells for the repair of segmental peripheral nerve defects*. He was also a Visiting Professor at Baylor College of Medicine where he spoke about the clinical application of modest hypothermia after acute cervical SCI.

Mark S. Nash, Ph.D., FACS

Professor, Neurological Surgery, Rehabilitation Medicine, & Physical Therapy

Laboratory Focus: Physiological Assessment of Secondary Complications following SCI: Electrical Stimulation, Cardiopulmonary Physiology and Exercise Biochemistry

Laboratory Summary: One of the enduring goals of The Miami Project has been to test and implement strategies that optimize the health of persons with SCI. One target of testing has focused on physical activity to lessen risks of the secondary complications associated with physical deconditioning. Outcomes of our studies support a role for exercise in improving fitness and cardiovascular functions, and lessening risks imposed by lipid disorders.



As population aging poses new health challenges, we have targeted some of our research to identify and intervene on these hazards in persons with SCI who are living beyond their 5th decade. This research has also examined the naturally-occurring decline in shoulder joint function that accompanies aging with SCI. Results have confirmed that exercise interventions are successful in reversing longstanding deconditioning and muscle weakness, and reducing shoulder pain. Subjects involved in these trials have also benefitted by improved cardiac function, and through blood lipid changes that slow the natural course of heart and vascular disease. This work holds great promise for improving health and function while reducing disease susceptibility. We have expanded this to validate inexpensive, home-based programs of fitness and testing of inexpensive medicines and non-drug agents that can reduce hazards of fasting lipid disorders and intake of high fat meals.

Notable Accomplishments: Dr. Nash presented results of his research at the Congress on Spinal Cord Medicine and Rehabilitation and was an invited speaker at the American Association of Physical Medicine and Rehabilitation. He presented a keynote address at the 4th International State-of-the-Art Congress "Rehabilitation: Mobility, Exercise, & Sports" in the Netherlands.

Jacqueline Sagen, Ph.D., M.B.A.**Professor, Neurological Surgery**

Laboratory Focus: Development of Improved Therapeutic Strategies in the Management of Chronic Spinal Cord Injury Pain

Laboratory Summary: Our laboratory continues to explore novel and more effective strategies in the therapeutic management of chronic debilitating pain. Our recent research is focused on: 1) identification of more effective analgesic agents and combinations for alleviating pain using SCI models and 2) development of emerging therapeutic interventions, including cell transplantation and gene therapy, which have the potential to provide long-term alleviation in people with intractable pain, overcoming the need for repeated pharmacologic administration. Recent findings in our laboratory have identified a drug that stimulates the cannabinoid receptor to effectively reduce pain responses in animals without developing tolerance to it, a common problem with current drugs prescribed for humans. Additionally, acetaminophen, which acts in part by inhibiting the degradation of naturally occurring cannabinoids in the body, in combination with morphine or gabapentin has a greater effect on reducing pain than either drug alone. We also discovered that 2 types of novel peptides derived from the marine cone snail were very effective, especially when given in combination, at reducing pain responses. These identified promising targets will be utilized in the generation of engineered cells and gene therapy vectors to produce sustained delivery of analgesic peptides. Our laboratory is currently pursuing several promising approaches towards this goal: 1) bone marrow stromal cells (BMSCs) as a vehicle for delivery of analgesic peptides, since they can be autologous and overcome limitations in human donor availability and immunologic mismatches, 2) neural stem cells, which can be selectively induced to differentiate towards an inhibitory (GABAergic) phenotype and additionally serve as a cellular replacement for lost or damaged inhibitory neurocircuitry in the injured spinal dorsal horn, and 3) viral vector-mediated delivery, which can specifically target spinal cord dorsal horn or spinal dorsal root ganglia to continuously produce engineered analgesic peptides for SCI pain.

Notable Accomplishments: Dr. Sagen was appointed as a peer reviewer for several granting agencies and foundations. She serves as Councilor for the American Society for Neural Therapy and Repair (ASNTR).

**Christine K. Thomas, Ph.D.****Professor, Neurological Surgery**

Laboratory Focus: Neuromuscular Weakness, Fatigue, Spasms, and Regeneration

Laboratory Summary: Our laboratory is currently asking two main questions. First, in studies on people with SCI, we want to understand how well involuntary contractions of paralyzed muscles (spasms) are managed by taking baclofen, a drug that is commonly used to control spasticity. Second, in our animal studies, we are exploring how to replace neurons that die because of SCI. Neuron death is common at the injury site and results in severe muscle weakness.

Since muscle spasms can occur throughout the day and night, and can be more of an issue in some muscles than others, we are making long-term (24-hour) recordings of electrical signals from various different paralyzed muscles simultaneously. This allows us to capture all of the contractions, to determine which contraction features make it more difficult for people with SCI to complete their daily activities, and whether use of baclofen improves this situation. The acute effects of baclofen are important to consider given that our recent results show chronic use of baclofen weakens muscles, which may result in long-term loss of function.

In our studies on rats, we have electrically stimulated neurons immediately after transplantation into peripheral nerve because neural depolarization is crucial for the survival of embryonic motoneurons and it may promote activity-dependent axon growth. Preliminary results show that more muscles were reinnervated from the transplanted neurons if the stimulation was provided for at least one hour. This intervention may facilitate rescue of weak, atrophied muscles from degeneration following denervation induced by SCI.

Notable Accomplishments: Dr. Thomas has presented her research at the annual Society for Neuroscience conference and at meetings that focus on how movements are generated and controlled.



Patrick M. Wood, Ph.D.**Research Professor, Neurological Surgery**

Laboratory Focus: Testing and Validation of Protocols for Use in the Manufacture of human Schwann Cells for FDA-Approved Clinical Applications; Cellular and Molecular Actions of cAMP and Neuregulin in Rat and Human Schwann Cells Underlying Axon Schwann Cell Interactions

Laboratory Summary: Schwann cells have shown promise in animal studies in promoting recovery from spinal cord injury. We have developed protocols that allow the generation, from a small biopsy of human peripheral nerve, of large numbers of a person's own Schwann cells that can be transplanted back into their injured spinal cord. We are nearing the final stages of testing and validation of all required Standard Operating Procedures (SOPs) that will be necessary for the manufacturing of human Schwann cells in accordance with FDA guidelines for clinical cell therapies. The SOPs are developed in accordance with the principles of Good Manufacturing Practice (GMP). An extensive characterization of the biological and molecular properties of these cells is underway. In parallel, and in collaboration with other investigators at The Miami Project, the Schwann cells generated by our SOPs are being tested for functional efficacy and safety by transplanting them into animal models of spinal injury.

Efficient growth of human Schwann cells in culture requires the addition of recombinant neuregulin and the cAMP enhancer forskolin. To better understand the effects of these reagents on Schwann cells, we are performing basic research to determine the mechanisms by which neuregulin and cAMP enhancers promote interaction between axons and Schwann cells, including axon-induced proliferation and the formation of myelin sheaths.

**John R. Bethea, Ph.D.****Associate Professor, Departments of Microbiology and Immunology and Neurological Surgery**

Laboratory Focus: Immunological Consequences of SCI and the Development of Neuroprotective Strategies

Laboratory Summary: In my laboratory we are studying spinal cord injury (SCI) and diseases of the nervous system such as Multiple Sclerosis (MS) to try to understand the cellular and molecular mechanisms that contribute to astrogliosis and secondary neuronal cell death. To this end, my laboratory has two main research objectives. First, we are studying the neuro-inflammatory response that occurs following SCI and secondly, we are developing novel therapies for SCI and diseases of the central nervous system.

To determine what role(s) trauma-induced inflammation plays in mediating secondary neuronal injury and cell death following SCI, we use transgenic mouse models and other molecular biological approaches. We have recently demonstrated that traumatic SCI initiates a very robust inflammatory response, both within the spinal cord and systemically. Specifically, we have shown that traumatic SCI activates NF- κ B within macrophages, microglia, endothelial cells and neurons. NF- κ B is a transcription factor that plays a pivotal role in regulating inflammation, and possibly apoptotic cell death pathways. We have recently generated mice that do not express functionally active NF- κ B in astrocytes and have determined that these mice are significantly protected from SCI and MS-induced paralysis, inflammation, and myelin damage.

The second major focus of my laboratory is to develop neuroprotective strategies for the treatment of acute SCI and MS. To this end, we perform high-content screening assays to try and identify novel regulators of NF- κ B activation and astrogliosis. The goal of these studies is to identify novel inhibitors of NF- κ B activation in astrocytes and test the neuroprotective potential in animal models of SCI and MS.



Nancy L. Brackett, Ph.D., HCLD**Research Associate Professor, Departments of Neurological Surgery and Urology****Laboratory Focus:** Male Fertility following Spinal Cord Injury

Laboratory Summary: Our research is focused on determining the cause of impaired semen quality in men with SCI. Our recent evidence indicates that the problem is related to the seminal plasma. Substances within the seminal plasma are abnormal in men with SCI, including elevated reactive oxygen species, decreased prostate specific antigen (a marker of prostate function), and decreased fructose (a marker of seminal vesicle function). The semen of men with SCI contains an abnormally high number of non-spermatozoon cells, most of which are leukocytes. Our current research is investigating inflammatory factors, including semen cytokine levels, as contributors to the problem. Our ultimate goal is to develop therapies to normalize semen quality in men with SCI, so that chances of biological fatherhood are increased.



We are also studying methods to improve semen retrieval and semen processing for assisted conception procedures. Recent improvements in treating male infertility in the general population have led to problems for men with SCI. Often, their ejaculates are not examined as a source of sperm for assisted reproductive technology (ART). Instead, sperm are retrieved surgically from their testes or epididymes as a first line treatment for anejaculation. This development has resulted in many centers performing expensive and invasive ART to overcome the low sperm numbers typically obtained with surgical sperm retrieval. Our research is focused on optimizing non-surgical methods of obtaining sperm from men with SCI and we are leading the field by establishing standards of care for treatment of infertility in men with SCI.

Notable accomplishments: Dr. Brackett is President of the Society for Male Reproduction and Urology.

Helen M. Bramlett, Ph.D.**Associate Professor, Department of Neurological Surgery****Laboratory Focus:** The Pathophysiology and Treatment of CNS Injury

Laboratory Summary: The focus of my neurotrauma laboratory is to investigate the importance of gender and progressive injury in models of brain and spinal cord trauma. Several recent studies have reported on the efficacy of hormones in treating stroke and traumatic brain injury. We have demonstrated endogenous neuroprotection from hormones in females compared to males on histopathological outcome measures. We are now focusing on the influence of the inflammatory response on outcome following TBI and the effect of hormones. In addition to studies in TBI, we are also studying the effects of hormones in attenuating damage and improving behavioral outcome after spinal cord injury (SCI). It may be advantageous to use estrogen in combination with other growth factors to facilitate regeneration after SCI.



Another project involves the recently discovered phenomenon of progressive injury after brain trauma. Current studies in the laboratory are designed to determine what mechanisms may be contributing to this progressive damage in order to design appropriate treatment strategies to halt this loss. Secondary hypoxia and hypotension frequently occur clinically after TBI. We have documented an exacerbation of histopathological damage as well as behavioral deficits following TBI and secondary hypoxia. Another factor that may play a critical role in traumatic outcome is the presence of a systemic inflammatory response secondary to multi-organ injury. We are currently concentrating on obtaining evidence for aggravated vascular dysfunction leading to an enhanced inflammatory response in our own polytrauma injury paradigm and testing novel therapeutic strategies to enhance recovery.

Notable Accomplishments: Dr. Bramlett was a Counselor for the National Neurotrauma Society and appointed as a member of the review committee for the NIH MBRS SCORE Neuroscience & Physiology Panel. She also spoke at the 7th Annual Pediatric Brain and Spinal Cord Injury Conference about *Sex Differences in CNS Injury and Recovery*.

James D. Guest, M.D., Ph.D.**Associate Professor, Neurological Surgery**

Laboratory Focus: Cellular and Molecular Strategies to Achieve Long Tract Regeneration in the Spinal Cord

Laboratory Summary: The current focus of my laboratory is on the transplantation of autologous glial cells to repair spinal cord injuries. We utilize several types of animal models with an emphasis on solving translational questions related to human clinical application. For example, we are using a pig model to develop the appropriate injection parameters for the transplantation of human Schwann cells. We are using a non-human primate model to evaluate the efficacy of autologous Schwann cell transplantation into a discrete pyramidal tract lesion. We also emphasize minimally-invasive surgical lesion-making and transplantation techniques. Sophisticated outcome assessment techniques are used to evaluate transplant effects in both the acute and chronic state of injury. These include kinematic assessment of hand function and gait, electrophysiologic study of conduction across lesion sites, and sensory testing. Other areas of research include studies of human post-mortem spinal cord tissue, intra-operative human spinal cord conduction studies, and research design for human clinical trials.

Notable accomplishments: Dr. Guest serves as center principal investigator for the North American Clinical Trials Network. He is also part of the International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP) leadership that wrote a position statement on the sale of unproven cellular therapies for SCI (*Spinal Cord* 47:713-714).

**Ian D. Hentall, Ph.D.****Research Associate Professor, Department of Neurological Surgery**

Laboratory Focus: Brainstem Stimulation for Spinal Injury; Serotonin in Spinal Motor and Sensory Control; Dietary Restriction; Brain Stimulation Techniques

Laboratory Summary: We work mainly on electrical brain stimulation as a way to improve general recovery from spinal cord injury (SCI) and traumatic brain injury (TBI). We see substantially improved functional and anatomical recovery in rats when we stimulate for about one week in a certain hindbrain region, starting within two days after a contusion in the thoracic spinal cord. We are currently studying the cellular mechanism of this effect, which we believe involves serotonin release in the spinal cord. We also found improved recovery from SCI after stimulating a midbrain area that is connected to the hindbrain ("raphé") region. This midbrain area has been safely stimulated in people to treat drug-resistant severe pain, so it offers a target for treating early SCI. A major part of our effort involves designing and fabricating novel, small, wireless stimulator implants for use in rodents, devices that also have potential uses in human neurotrauma. Separately, with the Miami Project's Dr. Helen Bramlett, we found that stimulating midbrain raphé regions early after TBI improves cognitive and motor recovery. These regions release serotonin in widespread forebrain regions. Putting the TBI and SCI results together, we propose that serotonin-containing brainstem regions function to control repair of neurotrauma. We also collaborate with several other Miami Project laboratories. With Dr. Brian Noga, we measure spinal cord levels of serotonin during locomotion using novel instrumentation that we developed in-house. With Dr. Jacqueline Sagen, we analyze how the electrical activity of spinal cord neurons is changed by nearby transplantation of analgesia-producing neuronal precursor cells. Finally, with Dr. Walter Hargraves of the University of Illinois, we study how dietary restriction affects spinal cord pathology, including SCI, finding that calorie restriction is not beneficial in the first weeks after SCI but does reduce chronic pain and arthritis in mice.



Gillian A. Hotz, Ph.D.

Associate Research Professor, Neurological Surgery; Co-Director, Pediatric Brain & SCI Program; Director, Neurotrauma Outcome Research, Concussion, WalkSafe™ & BikeSafe™ Programs

Laboratory Focus: Pediatric Brain Injury

Laboratory Summary: As a behavioral neuroscientist my clinical interests have always been investigating the neurocognitive deficits of those individuals that have sustained a traumatic and acquired brain injury. The best practice pediatric pedestrian program recognized by the National Safe Routes to School initiative is WalkSafe™. The program is an elementary school based pedestrian injury prevention program that has been shown to be effective in decreasing the number of children that are hit by cars in Miami-Dade County.



The WalkSafe™ program, developed in 2003, receives funding from a number of sources and pioneered the 5E model of education, engineering, enforcement, evaluation, and encouragement. We currently are piloting a BikeSafe™ program in Miami-Dade county. As the Director of the Concussion Program we have a comprehensive program including neuroimaging, neurologic evaluation, and neuropsychological testing. I am certified to administer IMPACT, a computerized neurocognitive screening test. We train high school and college trainers and coaches on a yearly basis.

Notable Accomplishments: During 2009, Dr. Hotz has had the opportunity to present at many conferences on the local, national and international levels. She is the lead author on the Pediatric Test of Brain Injury (2009), a neurocognitive test. She is a board member on a number of Advisory Groups and Associations, specifically Florida Injury Prevention Advisory Council, Florida Committee on Trauma, the Sarah Jane Brain Project, and the American Association of MultiSensory Environments.

Daniel J. Liebl, Ph.D.

Associate Professor, Neurological Surgery; Director, Neuroscience Graduate Program

Laboratory Focus: Function of Growth and Guidance Molecules in the Developing and Regenerating Nervous Systems

Laboratory Summary: The goal of my laboratory is to identify the mechanisms that lead to CNS pathophysiology and its regenerative potential. We focus on a family of molecules, called ephrins and Eph receptors, which play important roles in the developing, regenerating, and injured nervous systems. A choice tool in my laboratory is genetically altered mice, which provides important insight to the mechanisms that regulate traumatic brain and spinal cord injuries. Specifically, we are currently interested in the following areas: 1) Adult Neurogenesis: Understanding the mechanisms that regulate endogenous neurogenesis in the adult subventricular zone, and modifying cellular signals to attenuate these responses following CNS injury. We have discovered that ephrinB3 and its receptors are important regulators of neural progenitor cell proliferation, survival, and migration. 2) Neuroprotection: Identifying novel mechanisms of cell death and cues that initiate the early innate immune response following CNS injury. We have found that Eph receptors function as pro-apoptotic dependence receptors to regulate cell survival. 3) Synaptic plasticity: Examining synaptic integrity, degeneration, and synaptogenesis following injury, and the glial-neuronal interactions. We discovered that ephrins/Ephs play critical roles in control of synaptic function and plasticity. 4) Regeneration: Examining the mechanisms that regulate axonal growth, guidance, and bundling in both the developing and regenerating nervous systems. 5) Therapeutic strategies: Employing high-content screening to identify new and novel molecules that promote recovery, and translation of these findings to clinical trials. Overall, our approach is to develop novel strategies to minimize CNS damage and maximize regeneration, which can be best achieved through a comprehensive mechanistic approach.



Notable accomplishments: Dr. Liebl was a guest speaker at the 7th International Symposium on Experimental Spinal Cord Repair and Regeneration held in Brescia, Italy.

Alberto Martinez-Arizala, M.D.**Clinical Associate Professor, Neurology, Neurological Surgery, Orthopaedics, and Rehabilitation Medicine****Laboratory Focus:** Pathophysiology and Treatment of Spasticity and Pain in Spinal Cord Injury

Laboratory Summary: My research interests focus on two common complications that are seen following spinal cord injury: pain and spasticity. These two symptoms can be quite prominent in a significant number of people with SCI and can interfere with their daily activities and affect their quality of life. My interests include investigating the basis for the development of the different spasticity and pain profiles in the spinal cord injured population and to study potential novel treatments for those conditions.

We have established a very active and comprehensive Pain Team in The Miami Project in order to better characterize the types and causes of pain seen following spinal cord injury. The ultimate goal is to further our understanding of these disorders and to develop more effective treatments. To that end, the University of Miami/Jackson Memorial Medical Center is a major spinal cord injury center which provides health care for acutely spinal cord injured patients and for their comprehensive rehabilitation. This setting provides a significant population in which to study these disorders.

**Brian R. Noga, PH.D.****Research Associate Professor, Neurological Surgery****Laboratory Focus:** Brain and Spinal Mechanisms Controlling Walking and Nociception

Laboratory Summary: Our long-term goal is to develop new therapeutic strategies for enhancing spinal function following injury based on the delivery of neurotransmitters, similarly acting drugs, or transplantation of cells secreting these substances. Of the many possible neurotransmitter classes that could be used for this purpose, monoamines hold particular promise as a transmitter replacement candidate. Research from several laboratories support the idea that increased levels of spinal monoamines (serotonin and norepinephrine) can both facilitate locomotion and decrease pain following SCI. Therefore, we have concentrated our recent research effort on understanding the role these transmitters play in the production of locomotion and the control of pain. We have developed biosensors for the detection and measurement of these neurotransmitters to determine the patterns and timescales of release within the spinal cord following activation of the neuronal pathways that utilize them. These studies have shown that the release of these transmitters within the spinal cord is widespread during stimulation and dynamically regulated on a timescale of seconds. In contrast, highly localized spinal monoamine release observed in resting conditions (relevant for ongoing descending control of pain) may be regulated on a timescale of minutes. In all, these studies demonstrate that in order to affect spinal neurons, serotonin and norepinephrine may not have to be released directly at the synapse, the specialized structure between an axon and the nerve cell receiving its message. Instead, they can trigger transmission of messages when released anywhere around the nerve cells providing they can diffuse to target receptors located some distance from the site of its release. Our recent anatomical studies have demonstrated that spinal neurons mediating locomotor function are in close contact with terminals of descending monoaminergic pathways and possess serotonergic and noradrenergic receptors that can accomplish this task. These results imply that regeneration and repair strategies may not require restoration of direct (synaptic) connections in order to improve function. Therefore, duplicating such patterns of release will likely be important for the efficacy of transmitter enhancement strategies for improving locomotion and/or pain.

Notable Accomplishments: In 2009, Dr. Noga published important findings about locomotor-activated nerve cells in the cat in the *Journal of Neurophysiology* and was an ad hoc reviewer for the journal *Advances in Physiological Education*.



Damien D. Pearse, Ph.D.**Associate Professor, Department of Neurological Surgery****Laboratory Focus:** Exploration of Therapeutic Strategies to Repair the Injured Spinal Cord

Laboratory Summary: My laboratory focuses on several key aspects of CNS injury repair: 1) the utility of exogenous and endogenously harnessed cell therapeutics (particularly when used in combinatory approaches), 2) understanding the role of, and developing therapies for, altered cyclic AMP (adenylyl cyclase, phosphodiesterases, and PKA) and MAPK signaling in neurons and glia after CNS injury, 3) the use of nanotherapeutics for multifunctional and site-directed gene/drug targeting to the injured CNS, and 4) the application of methodologies for improved imaging of axonal regeneration and cell integration within the injured CNS such as 3D ultramicroscopy and diffusion tensor imaging.



Importantly, my laboratory has focused on performing studies essential to translating Schwann cell implantation and the delivery of the cyclic AMP modulating drug, Rolipram, to Phase 1/2 clinical trials in people with SCI. These studies have examined the safety and potential toxicity of these interventions as well as their optimization before clinical implementation. Primary among these experimental endeavors has been to (1) investigate the safety of Schwann cell implantation following both acute and chronic SCI, to determine if these cells enhance neuropathic pain, distribute to other organs, or form tumors when used as a therapy in clinically relevant models of injury and (2) identify the optimal methods for delivering Rolipram as a neuroprotective therapy for acute SCI by determining the best dose, route, and timing of its administration to achieve maximal tissue protection. We are producing critical data needed to submit an Investigational New Drug (IND) application to the Food and Drug Administration to request approval to begin a Phase 1/2 clinical trial to test Rolipram's safety and efficacy in acute human SCI.

Notable accomplishments: Dr. Pearse was promoted from Assistant to Associate Professor in 2009. Dr. Pearse received the following awards: A Mentor Recognition Award from The Leadership Alliance and The Sam Schmidt Paralysis/Sell Fund Young Investigator Award (Mentor).

Pantelis Tsoulfas, M.D.**Associate Professor, Departments of Neurological Surgery and Cell Biology & Anatomy****Laboratory Focus:** Neurotrophins: Specificity of Action

Laboratory Summary: My laboratory is interested in two areas of neurobiology that are significant for developing new strategies for spinal cord injury repair. Over the past years, we have worked to modify neurotrophins that are better suited for use in SCI. We are also interested in understanding the processes involved in maintaining and differentiating neural stem cells.

For SCI repair strategies, my lab utilizes modified neurotrophins and grafting of CNS derived cells. Several approaches are integrated, including Cell Biology, Molecular Biology, Biochemistry, Genetics, and Imaging techniques. In our project related to modifying neurotrophins, we were able to improve the specificity of binding to the Trk receptors and eliminate the negative effects mediated through p75NTR. These new neurotrophins improved the grafting of Schwann cells and regeneration of several fiber tracts in the spinal cord. The implications of these studies are that these new modified neurotrophins are better suited for animal studies.



For the development of the nervous system, my lab strives to understand how mitogenic factors influence cell numbers and how cell fates are linked to specific transcriptional networks. We discovered a new mechanism for neural stem cell expansion and maintenance. This mechanism involves the degradation SCF(SKP2) complex. We also discovered a set of transcription factors that might be involved in regulating neural progenitor proliferation during CNS development.

Eva Widerström-Noga, D.D.S., Ph.D.

Research Associate Professor, Neurological Surgery, Rehabilitation Medicine, and Neuroscience Program, and the Veterans Administration

Laboratory Focus: Chronic Pain and Altered Sensation following SCI

Laboratory Summary: Research topics in my laboratory relate to the evaluation of physiological and psychological mechanisms for the generation and maintenance of persistent pain conditions after SCI. Our main areas of interest are:

1. Evaluation of sensory dysfunction

Sensory dysfunction following SCI is clinically manifested as both spontaneous and evoked sensations. Spontaneous neuropathic pain, evoked pain, and motor excitability may share common mechanisms, such as neuronal hyperexcitability due to loss of input to certain populations of neurons or lack of inhibition. In order to better elucidate such mechanisms, we perform quantitative sensory testing (QST) in the evaluation of these pain conditions.

2. Evaluation of psychosocial impact

The refractory nature of the painful conditions following SCI suggests that personal characteristics related to adaptation and coping skills are critical determinants for quality of life. Despite seemingly similar pain conditions, clinical observation suggests that there is wide variability in how people respond to treatment interventions and adapt to SCI-related pain. To address this, we are developing and psychometrically testing various methods for the evaluation of the psychosocial impact of pain.

3. Determining thalamic and cortical pain-generating mechanisms

Neuroimaging studies strongly suggest that pain perception is dependent on a network of sensory cortical areas (primary and secondary somatosensory cortices, insular cortex), limbic areas (anterior cingulate), associative cortex (prefrontal cortex), and subcortical structures, such as the thalamus. Dysfunction in these networks may underlie the generation and maintenance of chronic pain and associated conditions. We are conducting imaging studies to assess neuronal function in the thalamus and areas of the cingulate cortex in individuals with neuropathic pain and SCI.

Notable Accomplishments: Dr. Widerström-Noga gave a keynote lecture at the Congress on Spinal Cord Medicine and Rehabilitation. She also moderated a workshop entitled *Assessment and classification of SCI-related pain: basic and clinical perspectives*. She was appointed Chair of the Miami VA Research & Development Committee.

**Coleen Atkins, Ph.D.**

Assistant Professor, Neurological Surgery

Laboratory Focus: Developing Novel Therapies for Traumatic Brain Injury and Spinal Cord Injury

Laboratory Summary: The research in my laboratory focuses on developing novel therapeutic interventions for traumatic brain injury (TBI) and spinal cord injury (SCI). Promoting recovery after TBI or SCI through rehabilitation is a very promising research area that has already resulted in significant benefits to people with paralysis. The research goal of my laboratory is to enhance rehabilitation and recovery by manipulating synaptic plasticity at specific levels of the neuroaxis following SCI. We have initiated preliminary studies assessing the cellular signaling pathways that are involved in synaptic plasticity at supraspinal regions after SCI, and this will be an important research direction in which we will test novel strategies to enhance recovery after SCI.

Notable Accomplishments: In 2009, Dr. Atkins was promoted from Lecturer to Assistant Professor and received an NIH-funded R21 grant.



Murray Blackmore, Ph.D.**Research Assistant Professor, Neurological Surgery**

Laboratory Focus: Gene Therapy Strategy to Boost the Intrinsic Ability of Neurons to Regenerate Axons after Spinal Cord Injury.

Laboratory Summary: The goals of my laboratory are to clarify the molecular mechanisms that control the growth of axons from nerve cells, and to harness that information to create novel therapies for nervous system injury. Taking advantage of recent advances in automated microscopy, we use high content analysis to rapidly test hundreds of candidate genes in cultured neurons. These culture experiments identify novel genes that can block or stimulate axon outgrowth. Because we believe that combinations of genes will be most effective, we work to develop molecular tools that can overexpress and/or knock down multiple gene targets in a single cell. We are currently testing candidate genes in a model of spinal cord injury in rodents. We use lentiviral particles to deliver our overexpression or knockdown constructs to corticospinal motor neurons, and then assess whether these gene manipulations promote axon regeneration after spinal injury.

Notable Accomplishments: Dr. Blackmore is one of our newly appointed faculty members during 2009.

**Paula V. Monje, Ph.D.****Lecturer, Neurological Surgery**

Laboratory Focus: Neuron-Glia interactions in the regulation of Schwann cell proliferation and myelination; signal transduction mechanisms of cAMP and receptor tyrosine kinase signaling

Laboratory Summary: Transplantation of Schwann cells, the myelinating glia of the peripheral nervous system, has demonstrated promising potential as a strategy to enhance regeneration and myelination of central nervous system axons in experimental models of spinal cord injury. In addition, the repairing effect of transplanted Schwann cells can be significantly enhanced by co-administration of agents increasing the intracellular levels of the cyclic nucleotide cAMP. In this context, my lab is currently investigating the functional role of cAMP as a second messenger system in the reciprocal interactions between Schwann cells and axons underlying:

1. The axonal regulation of Schwann cell proliferation and myelination during development and
2. The control of Schwann cell de-differentiation, cell cycle re-entry and re-myelination after injury.

For this, we are making use of the tools and concepts of the signal transduction field in combination with cell culture models of neurons and glia to dissect basic underlying regulatory mechanisms at the molecular level. Special emphasis is put on the role of signaling cross-talk between cAMP and receptor tyrosine kinases, including signaling mediated by ErbB/HER receptors and neuregulin, a known crucial regulator of Schwann cell development. Our improved understanding of the interactions between neurons and Schwann cells will help to identify molecular targets amenable to pharmacological/genetic intervention in the treatment of diseases of the myelin and in cellular therapy involving Schwann cell transplantation.

Notable Accomplishments: Dr. Monje is one of our newly appointed faculty members during 2009.



The Miami Project Education Department has stepped into the “cyber” age and has been hosting a distance learning program with a high school in Virginia. The **Mountain Vista Governor’s School** provides a research-based, technology-based, integrated program in math, science, and humanities for gifted and talented junior and high school students and their two campuses are in Fauquier and Frederick, Virginia, at the Lord Fairfax Community College. The school serves school districts in 7 counties in Virginia. The goal of their program is to “challenge students to reach their full potential as independent thinkers capable of assuming leadership roles in a constantly changing global society”.

The distance learning program began in 2007 thanks to Dr. Dalton Dietrich and his brother, **John Dietrich**, who is the lead **Research Instructor** at Mountain Vista. When John Dietrich began his position at Mountain Vista 2 ½ years ago, the goal was to use distance learning technology only between the two Mountain Vista campuses. With his Masters degree in *Curriculum and Technology* and in conjunction with his brother Dalton, and Dalton’s wife Helen, and the education department at The Miami Project, they have taken the curriculum to new dimensions this year with the most professional support from the educational coordinators, expert technical staff, and competent research scientists.

The curriculum covers multiple aspects of neurotrauma research, the specialty of The Miami Project. The first lecture was in December 2009 in which Dr. Kim Anderson-Erisman gave an **overview** of spinal cord injury, the basic mechanisms of repair, and the clinical trial process utilized to translate scientific discoveries. In January 2010, Dr. Coleen Atkins gave a lecture on **neuroprotection** research and utilized hypothermia as an example of a therapeutic intervention. Dr. Damien Pearse lectured about **cell replacement** strategies in February using many examples from his Schwann cell transplantation studies as well as his olfactory ensheathing glia cell transplantation studies. In March, Dr. Helen Bramlett will give a lecture discussing **neuroregeneration** and **neurodegeneration**, using examples from her research on progressive atrophy of brain structures following trauma to highlight opportunities for therapeutic interventions. In April the curriculum will switch gears and start addressing long-term clinical problems associated with chronic paralysis of the central nervous system. Dr. Edelle Field-Fote will talk about **neurorehabilitation** research and how different training protocols promote functional recovery in a differential manner. Dr. Christine Thomas will discuss **neural**



John Dietrich’s Mountain Vista Governor’s School students

plasticity, changes or adaptations in the nervous system that occur with time post-injury, and how her research is discovering unique changes in neuromuscular properties associated with muscle spasticity. The curriculum will conclude with Dr. Mark Nash giving a lecture about the **neurophysiological** changes that occur post-injury and how his research utilizing exercise conditioning can improve cardiovascular, cardiopulmonary, and metabolic function.

The students are required to do background research on issues associated with The Miami Project to Cure Paralysis prior to each distance learning session. They are required to critically think about these issues and formulate questions. It is a challenge that the students are ready to take head-on. “It amazes me how much, we in the science field, take for granted regarding what these young people know and have been exposed to in life. My students have commented on how fortunate they feel to have this opportunity to learn first-hand, with real scientists, especially in a synchronous environments”, states John Dietrich. They have discussed the often heard about situation in education that deals with a decline in our American youth in the field of math and science. Distance learning is something that their junior and senior high school students will be exposed to more when they go off to college. This opportunity has already demonstrated success as many of their student graduates have commented on its benefits.

Thanks to technological advances in telecommunications, the expert support from the University of Miami medical information technology staff, and the dedicated support of The Miami Project A/V team, we are able to teach young people around the country about the complexity and importance of neurotrauma research. As this outreach program progresses we plan on recording the lectures and creating a teaching DVD that can be sent to other schools to use as an advanced teaching tool and encourage the next generation to pursue careers in science and to discover treatments for the vast amount of neurologic disorders that impact people’s lives. 🇺🇸

Published studies that have passed the test of peer review are the benchmark of scientific progress. Listed here are the research publications by Miami Project scientists and colleagues for 2009.

To find links to the abstracts and complete scientific publications listed here, visit the Research Publications section of our website at www.themiamiproject.org/researchpublications



Abulafia DP, de R, V, Lozano JD, Lotocki G, Keane RW, Dietrich WD (2009). **Inhibition of the inflammasome complex reduces the inflammatory response after thromboembolic stroke in mice.** J Cereb Blood Flow Metab 29:534-544.

Alexander MS, Brackett NL, Bodner D, Elliott S, Jackson A, Sonksen J (2009). **Measurement of sexual functioning after spinal cord injury: preferred instruments.** J Spinal Cord Med 32:226-236.

Alexander MS, Biering-Sorensen F, Bodner D, Brackett NL, Cardenas D, et al. (2009). **International standards to document remaining autonomic function after spinal cord injury.** Spinal Cord 47:36-43.

Arvanian VL, Schnell L, Lou L, Golshani R, Hunanyan A, Arko G, Pearse DD, Robinson JK, Schwab ME, Fawcett JW, Mendell LM (2009). **Chronic spinal hemisection in rats induces a progressive decline in transmission in uninjured fibers to motoneurons.** Experimental Neurology 216:471-480.

Atkins CM, Falo MC, Alonso OF, Bramlett HM, Dietrich WD (2009). **Deficits in ERK and CREB activation in the hippocampus after traumatic brain injury.** Neurosci Lett 459:52-56.

Bathen M, Smith JS, Levi AD, Stewart O, Gupta R (In press). **Advances in the Management of Acute Spinal Cord Injury.** Journal of the American Academy of Orthopaedic Surgery.

Benglis D, Levi AD (In press). **Neurological findings of craniovertebral junction diseases. Surgery of the Craniovertebral Junction.** Neurosurgery.

Benglis D, Levi AD (In press). **Robotics, FES, brain-computer interfaces, locomotor training strategies. In Management of spine and spinal cord trauma: an evidence based analysis.** (eds. Vaccaro AR, Fehlings MG, Dvorak M) Thieme medical publishers, Inc. Chapter 55.

Benglis DM, Vanni S, Levi AD (2009). **An anatomical study of the lumbosacral plexus as related to the minimally invasive transposas approach to the lumbar spine.** J Neurosurg Spine 10:139-144.

Bigford GE, Alonso OF, Dietrich WD, Keane RW (2009). **A Novel Protein Complex In Membrane Rafts Linking The Nr2b Glutamate Receptor And Autophagy Is Disrupted Following Traumatic Brain Injury.** J. Neurotrauma. 26:703-720.

Blight A, Curt A, Ditunno JF, Dobkin B, Ellaway P, Fawcett J, Fehlings M, Grossman RG, Lammertse DP, Privat A, Steeves J, Tuszynski M, Kalichman M, Guest JD (2009). **Position statement on the sale of unproven cellular therapies for spinal cord injury: the international campaign for cures of spinal cord injury paralysis.** Spinal Cord 47:713-714.

Bonfield CM, Levi AD, Arnold PM, Okonkwo DO. (In press). **Surgical management of posttraumatic syringomyelia after spinal cord injury.** Spine.

Bono M, Schoenfeld A, Rampersaud R, Levi AD, Grauer J, Arnold P, Fehlings MG, Dvorak M, Vaccaro AR (In press). **The reproducibility of radiographic measurements for subaxial cervical spine trauma.** Spine J.

Brackett NL, Ibrahim E, Iremashvili V, Aballa TC, Lynne CM (In press). **Treatment of**

ejaculatory dysfunction in men with spinal cord injury: a single-center experience of more than 18 years. J Urol.

Brackett NL, Ohl DA, Sønksen J, Lynne CM (2009). **Abnormalities of ejaculation.** In: *Infertility in the Male, 4th edition*, L Lipshultz, S Howards C. Niederberger (eds). Cambridge University Press, Cambridge, 454-473.

Brackett NL, Ibrahim E (2009). **Fertility after spinal cord injury.** In: *Spinal Cord Injury Rehabilitation*, E Field-Fote (ed). FA Davis Co., Philadelphia, 531-547.

Brambilla R, Hurtado A, Persaud T, Esham K, Pearse DD, Oudega M, Bethea JR (2009). **Transgenic inhibition of astroglial NF-kappa B leads to increased axonal sparing and sprouting following spinal cord injury.** J Neurochem 110:765-778.

Brambilla R, Persaud T, Hu X, Karmally S, Shestopalov VI, Dvorianchikova G, Ivanov D, Nathanson L, Barnum SR, Bethea JR (2009). **Transgenic inhibition of astroglial NF-kappa B improves functional outcome in experimental autoimmune encephalomyelitis by suppressing chronic central nervous system inflammation.** J Immunol 182:2628-2640.

Bramlett HM, Furones-Alonso O, Lotocki G, Rodriguez-Paez A, Sanchez-Molano J, Keane RW (2009). **Sex differences in XIAP cleavage after traumatic brain injury in the rat.** Neurosci Lett 461:49-53.

Bullock MR (2009). **Editorial.** J Neurosurg. Published online October 23, DOI: 10.3171/2009.8.JNS091108.

Bunge MB, Wood PM (In press). **Realizing the maximum potential of Schwann cells to promote recovery from spinal cord**

injury. Chapter 34 in Handbook of Clinical Neurology, Spinal Cord Trauma, 3rd Edition (J Verhaagan, JW McDonald, Eds), Elsevier, N.Y.

Calancie B, Madsen PW, Wood P, Marcillo AE, Levi AD, Bunge RP (2009). **A guidance channel seeded with autologous Schwann cells for repair of cauda equina injury in a primate model.** J Spinal Cord Med 32:379-388.

Cardenas DD, Hoffman JM (2009). **Hydrophilic catheters versus noncoated catheters for reducing the incidence of urinary tract infections: a randomized controlled trial.** Arch Phys Med Rehabil 90:1668-1671.

Cardenas DD, Felix ER (2009). **Pain after spinal cord injury: a review of classification, treatment approaches, and treatment assessment.** PMR 1:1077-1090.

Cowan RE, Malone LA, Nash MS (2009). **EXERCISE is Medicine®: Exercise Prescription after SCI to Manage CVD Risk Factors.** Top Spinal Cord Inj Rehabil 14:69-83.

Cowan RE, Nash MS, Collinger JL, Koontz AM, Boninger ML (2009). **Impact of surface type, wheelchair weight, and axle position on wheelchair propulsion by novice older adults.** Arch Phys Med Rehabil 90:1076-1083.

Cruz-Almeida Y, Felix ER, Martinez-Arizala A, Widerstrom-Noga EG (2009). **Pain symptom profiles in persons with spinal cord injury.** Pain Med 10:1246-1259.

Cruz-Almeida Y, Alameda G, Widerstrom-Noga EG (2009). **Differentiation between pain-related interference and interference caused by the functional impairments of spinal cord injury.** Spinal Cord 47:390-395.

de Rivero Vaccari JP, Lotocki G, Alonso OF, Bramlett HM, Dietrich WD, Keane RW (2009). **Therapeutic neutralization of the NLRP1 inflammasome reduces the innate immune response and improves histopathology after traumatic brain injury.** J Cereb Blood Flow Metab 29:1251-1261.

de Rivero Vaccari JP, Marcillo A, Nonner D, Dietrich WD, Keane RW (2009). **Neuroprotective effects of bone morphogenetic protein 7 (BMP7) treatment after spinal cord injury.** Neurosci Lett 465:226-229.

Dietrich WD (2009). **A tribute to Dr. Hubert L. Rosomoff: a pioneer in treatment of pain and use of hypothermia.** J Neurotrauma 26:299-300.

Dietrich WD, Bullock MR, Kochanek PM (2009). **Hypothermic therapies targeting brain and spinal cord injury. Introduction.** J Neurotrauma 26:297-298.

Dietrich WD, Atkins CM, Bramlett HM (2009). **Protection in animal models of brain and spinal cord injury with mild to moderate hypothermia.** J Neurotrauma 26:301-312.

Dietrich WD, III (2009). **Therapeutic hypothermia for spinal cord injury.** Crit Care Med 37:S238-S242.

Dvorianchikova G, Barakat D, Brambilla R, Agudelo C, Hernandez E, Bethea JR, Shestopalov VI, Ivanov D (2009). **Inactivation of astroglial NF-kappaB promotes survival of retinal neurons following ischemic injury.** Eur J Neurosci 30:175-185.

Farhat HI, Hood B, Bullock MR (2009). **A tangential gunshot wound to the head: Case report and review of the literature.** J Emerg Med. Published online December 21, DOI:10.1016/J.JEMERMED.2009.10.015

Felix ER, Widerstrom-Noga EG (2009). **Reliability and validity of quantitative sensory testing in persons with spinal cord injury and neuropathic pain.** J Rehabil Res Dev 46:69-83.

Field-Fote EC (2009). **Affirming the fundamentals in an age of high-tech rehabilitation.** J Neurol Phys Ther 33:127-128.

Field-Fote EC (2009). **Editor's note: the power of words.** J Neurol Phys Ther 33:67.

Fortun J, Hill CE, Bunge MB (2009). **Combinatorial strategies with Schwann cell transplantation to improve repair of the injured spinal cord.** Neurosci Lett 456:124-132.

Fortun J, Puzis R, Pearse D, Gage FH, Bunge MB (2009). **Muscle injection of AAV-NT3 promotes anatomical reorganization of CST axons and improves behavioral outcome following SCI.** J Neurotrauma 26:941-953.

Fouad K, Ghosh M, Vavrek R, Tse AD, Pearse DD (2009). **Dose and chemical modification considerations for continuous cyclic AMP analog delivery to the injured CNS.** J Neurotrauma 26:733-740.

Fouad K, Pearse DD, Tetzlaff W, Vavrek R (2009). **Transplantation and repair: combined cell implantation and chondroitinase delivery prevents**

deterioration of bladder function in rats with complete spinal cord injury. Spinal Cord 47:727-732.

Fu ES, Zhang YP, Candiotti KA, Sagen J, Morton PD, Liebl DJ, Bethea JR, Brambilla R (In press). **Transgenic Inhibition of Glial NF-kappa B Reduces Pain Behavior and Inflammation after Peripheral Nerve Injury.** Pain.

Furmanski O, Gajavelli S, Lee JW, Collado ME, Jergova S, Sagen J (2009). **Combined extrinsic and intrinsic manipulations exert complementary neuronal enrichment in embryonic rat neural precursor cultures: an in vitro and in vivo analysis.** J Comp Neurol 515:56-71.

Furne C, Ricard J, Cabrera JR, Pays L, Bethea JR, Mehlen P, Liebl DJ (2009). **EphrinB3 is an anti-apoptotic ligand that inhibits the dependence receptor functions of EphA4 receptors during adult neurogenesis.** Biochim Biophys Acta 1793:231-238.

Gonzalez-Brito MR, Bixby JL (2009). **Protein tyrosine phosphatase receptor type O regulates development and function of the sensory nervous system.** Mol Cell Neurosci 42:458-465.

Groah SL, Nash MS, Ljungberg IH, Libin A, Hamm LF, Ward E, Burns PA, Enfield G (2009). **Nutrient intake and body habitus after spinal cord injury: an analysis by sex and level of injury.** J Spinal Cord Med 32:25-33.

Grumbles RM, Sesodia S, Wood PM, Thomas CK (2009). **Neurotrophic factors improve motoneuron survival and function of muscle reinnervated by embryonic neurons.** J Neuropathol Exp Neurol 68:736-746.

Hama A, Sagen J (2009). **Sustained antinociceptive effect of cannabinoid receptor agonist WIN 55,212-2 over time in rat model of neuropathic spinal cord injury pain.** J Rehabil Res Dev 46:135-143.

Hama A, Sagen J (2009). **Antinociceptive effects of the marine snail peptides conantokin-G and conotoxin MVIIA alone and in combination in rat models of pain.** Neuropharmacology 56:556-563.

Hama AT, Sagen J (2009). **Cannabinoid receptor-mediated antinociception with acetaminophen drug combinations in rats with neuropathic spinal cord injury pain.** Neuropharmacology. December 24, doi:10.1016/j.neuropharm.2009.12.010.

Harper MM, Adamson L, Blits B, Bunge MB, Grozdanic SD, Sakaguchi DS (2009). **Brain-derived neurotrophic factor released from engineered mesenchymal stem cells attenuates glutamate- and hydrogen peroxide-mediated death of staurosporine-differentiated RGC-5 cells.** *Exp Eye Res* 89:538-548.

Hartings JA, Strong AJ, Fabricius M, Manning A, Bhatia R, Dreier JP, Mazzeo AT, Tortella FC, Bullock MR (2009). **Spreading depolarizations and late secondary insults after traumatic brain injury.** *J Neurotrauma* 26:1857-1866.

Hentall ID, Burns SB (2009). **Restorative effects of stimulating medullary raphe after spinal cord injury.** *J Rehabil Res Dev* 46:109-122.

Hood B, Levene HB, Levi AD (2009). **Transplantation of autologous Schwann cells for the repair of segmental peripheral nerve defects.** *Neurosurg Focus* 26:E4.

Hotz G, de Marcilla AG, Lutfi K, Kennedy A, Castellon P, Duncan R. (2009). **The WalkSafe Program: developing and evaluating the educational component.** *J Trauma* 66(3 Suppl):S3-9.

Hotz G, Helm-Estabrooks N, Wolf Nelson N, Plante E (2009). **The Pediatric Test of Brain Injury: Development and Interpretation.** *Topics in Language Disorders* 29:207-223.

Hotz G, Kennedy A, Lutfi K, Cohn SM. (2009). **Preventing pediatric pedestrian injuries.** *J Trauma* 66:1492-1499.

Hower AE, Beltran PJ, Bixby JL (2009). **Dimerization of tyrosine phosphatase PTPRO decreases its activity and ability to inactivate TrkC.** *J Neurochem* 110:1635-1647.

Huang T, Solano J, He D, Loutfi M, Dietrich WD, Kuluz JW (2009). **Traumatic injury activates MAP kinases in astrocytes: mechanisms of hypothermia and hyperthermia.** *J Neurotrauma* 26:1535-1545.

Ibrahim E, Brackett NL, Aballa TC, Lynne CM (2009). **Safety of a novel treatment to improve sperm motility in men with spinal cord injury.** *Fertil Steril* 91:1411-1413.

Iremashvili VV, Brackett NL, Ibrahim E, Aballa TC, Lynne CM (In press). **A minority of men with spinal cord injury have normal semen quality. Can we learn from them? A case-control study.** *Urol*.

Jensen MP, Widerstrom-Noga E, Richards JS, Finnerup NB, Biering-Sorensen F, Cardenas DD (2009). **Reliability and validity of the International Spinal Cord Injury Basic Pain Data Set items as self-report measures.** *Spinal Cord*. September 29, DOI:10.1038/sc.2009.112.

Jensen MP, Barber J, Romano JM, Hanley MA, Raichle KA, Molton IR, Engel JM, Osborne TL, Stoelb BL, Cardenas DD, Patterson DR (2009). **Effects of self-hypnosis training and EMG biofeedback relaxation training on chronic pain in persons with spinal-cord injury.** *Int J Clin Exp Hypn* 57:239-268.

Klein CS, Peterson LB, Ferrell S, Thomas CK (2009). **Sensitivity of 24 hour EMG duration and intensity in the human vastus lateralis muscle to threshold changes.** *J Appl Physiol*. December 10, DOI:10.1152/jappphysiol.00757.2009.

Krajacic A, Ghosh M, Puentes R, Pearse DD, Fouad K (2009). **Advantages of delaying the onset of rehabilitative reaching training in rats with incomplete spinal cord injury.** *Eur J Neurosci* 29:641-651.

Kuluz J, Samdani A, Benglis D, Gonzalez-Brito M, Solano J, Ramirez M, Luqman A, De Los Santos R, Hutchinson D, Nares M, Padgett K, He D, Huang T, Levi AD, Betz R, Dietrich WD (In press). **New large animal model of pediatric spinal cord injury.** *J Spinal Cord Med*.

Levene H, Nimmigada A, Levi AD (In press). **An unusual case of foot drop. Anterior lumbar disc herniation mimicking a nerve sheath tumor.** *Neurosurgery*.

Levi AD, Casella G, Green BA, Dietrich WD, Vanni S, Jagid J, Wang MW (In press). **Clinical outcomes using modest intravascular hypothermia after acute cervical spinal cord injury.** *Neurosurgery*.

Levi AD, Green BA, Wang MY, Dietrich WD, Brindle T, Vanni S, Casella G, Elhammady G, Jagid J (2009). **Clinical application of modest hypothermia after spinal cord injury.** *J Neurotrauma* 26:407-415.

Levi AD, Ross AL, Cuartas JE, Qadir R, Temple T (In press). **Surgical management of symptomatic peripheral nerve sheath tumors.** *Neurosurgery*.

Lo TP, Jr., Cho KS, Garg MS, Lynch MP, Marcillo AE, Koivisto DL, Stagg M, Abail RM, Patel S, Dietrich WD, Pearse DD (2009). **Systemic hypothermia improves**

histological and functional outcome after cervical spinal cord contusion in rats. *J Comp Neurol* 514:433-448.

Lotocki G, de Rivero Vaccari JP, Perez ER, Sanchez-Molano J, Furones-Alonso O, Bramlett HM, Dietrich WD (2009). **Alterations in blood-brain barrier permeability to large and small molecules and leukocyte accumulation after traumatic brain injury: effects of post-traumatic hypothermia.** *J Neurotrauma* 26:1123-1134.

Marion D, Bullock MR (2009). **Current and future role of therapeutic hypothermia.** *J Neurotrauma* 26:455-67.

Massa LM, Hoffman JM, Cardenas DD (2009). **Validity, accuracy, and predictive value of urinary tract infection signs and symptoms in individuals with spinal cord injury on intermittent catheterization.** *J Spinal Cord Med* 32:568-573.

Mazzeo AT, Brophy GM, Gilman CB, Alves OL, Robles JR, Hayes RL, Povlishock JT, Bullock MR (2009). **Safety and tolerability of cyclosporin a in severe traumatic brain injury patients: results from a prospective randomized trial.** *J Neurotrauma* 26:2195-2206.

Mazzeo AT, Beat A, Singh A, Bullock MR (2009). **The role of mitochondrial transition pore, and its modulation, in traumatic brain injury and delayed neurodegeneration after TBI.** *Exp Neurol* 218:363-370.

McCluggage LK, Voils SA, Bullock MR (2009). **Phenytoin toxicity due to genetic polymorphism.** *Neurocrit Care* 10:222-224.

Molton IR, Stoelb BL, Jensen MP, Ehde DM, Raichle KA, Cardenas DD (2009). **Psychosocial factors and adjustment to chronic pain in spinal cord injury: replication and cross-validation.** *J Rehabil Res Dev* 46:31-42.

Monje PV, Rendon S, Athauda G, Bates M, Wood PM, Bunge MB (2009). **Non-antagonistic relationship between mitogenic factors and cAMP in adult Schwann cell re-differentiation.** *Glia* 57:947-961.

Moore DL, Blackmore MG, Hu Y, Kaestner KH, Bixby JL, Lemmon VP, Goldberg JL (2009). **KLF family members regulate intrinsic axon regeneration ability.** *Science* 326:298-301.

Nash MS (2009). **Cardiovascular Disease after SCI.** *Top Spinal Cord Inj Rehabil* 14:vi-vii.

Nash, M.S. (2009). **Cardiovascular Health and Exercise Prescription**. In: Spinal Cord Injury Rehabilitation, E. Field-Fote (Ed.), pp. 411-27. Contemporary Perspectives in Rehabilitation (S.L.Wolf, Series Editor). F.A. Davis, Co., Philadelphia, PA.

Nash MS, Dyson-Hudson T (2009). **Guideline-Driven Assessment of Cardiovascular Disease and Related Risks after SCI**. Top Spinal Cord Inj Rehabil 14:32-45.

Nash MS, Mendez AJ (2009). **Non-Fasting Lipemia and Inflammation as Cardiovascular Disease Risks after SCI**. Top Spinal Cord Inj Rehabil 14:32-45.

Ness LL, Field-Fote EC (2009). **Whole-body vibration improves walking function in individuals with spinal cord injury: a pilot study**. Gait Posture 30:436-440.

Ness LL, Field-Fote EC (2009). **Effect of whole-body vibration on quadriceps spasticity in individuals with spastic hypertonia due to spinal cord injury**. Restor Neurol Neurosci. 2009;27:621-631.

Noga BR, Johnson DM, Riesgo MI, Pinzon A (2009). **Locomotor-activated neurons of the cat. I. Serotonergic innervation and co-localization of 5-HT7, 5-HT2A, and 5-HT1A receptors in the thoraco-lumbar spinal cord**. J Neurophysiol 102:1560-1576.

Nooijen CF, Ter HN, Field-Fote EC (2009). **Gait quality is improved by locomotor training in individuals with SCI regardless of training approach**. J Neuroeng Rehabil 6:36.

Ohl DA, Quallich SA, Sonksen J, Brackett NL, Lynne CM (2009). **Anejaculation: an electrifying approach**. Semin Reprod Med 27:179-185.

Ohl DA, Quallich SA, Sonksen J, Brackett NL, Lynne CM (In press). **Ejaculation induction procedures: penile vibratory stimulation and electroejaculation**. In: *Glenn's Urologic Surgery, 7th edition*. SD Graham, TE Keane, JF Glenn (eds). Macmillan Publishers, Beverly, MA.

Padayachy LC, Figaji AA, Bullock MR (2009). **Intracranial pressure monitoring for traumatic brain injury in the modern era**. Childs Nerv Syst. November 24, DOI 10.1007/s00381-009-1034-0.

Raffa SJ, Benglis DM, Levi AD (2009). **Treatment of a persistent iatrogenic cerebrospinal fluid-pleural fistula with a cadaveric dural-pleural graft**. Spine J 9:e25-e29.

Raval AP, Saul I, Dave KR, DeFazio RA, Perez-Pinzon MA, Bramlett H. (2009). **Pretreatment with a single estradiol-17beta bolus activates cyclic-AMP response element binding protein and protects CA1 neurons against global cerebral ischemia**. Neuroscience 160:307-318.

Richardson RM, Singh A, Sun D, Fillmore HL, Dietrich DW, Bullock MR (2009). **Stem cell biology in traumatic brain injury: effects of injury and strategies for repair**. J Neurosurg. June 5, DOI: 10.3171/2009.4.JNS081087.

Sheth RN, Manzano G, Levi AD (2009). **Post-Traumatic Syringomyelia**. In Cervical Spine Trauma (eds. Vaccaro, Anderson (co-ed)) Lippincott Williams & Wilkins. Chapter 38 pp 551-558, 2009.

Sun D, Bullock MR, McGinn MJ, Zhou Z, Altememi N, Hagood S, Hamm R, Colello RJ (2009). **Basic fibroblast growth factor-enhanced neurogenesis contributes to cognitive recovery in rats following traumatic brain injury**. Exp Neurol 216:56-65.

Tapanes-Castillo A, Weaver EJ, Smith RP, Kamei Y, Caspary T, Hamilton-Nelson KL, Slifer SH, Martin ER, Bixby JL, Lemmon VP (2009). **A modifier locus on chromosome 5 contributes to L1 cell adhesion molecule X-linked hydrocephalus in mice**. Neurogenetics. June 30, DOI 10.1007/s10048-009-0203-3.

Tolias CM, Kumaria A, Bullock MR (2009). **Hyperoxia and traumatic brain injury**. J Neurosurg 110:607-609.

Tran ND, Kim S, Vincent HK, Rodriguez A, Hinton DR, Bullock MR, Young HF (2009). **Aquaporin-1-mediated cerebral edema following traumatic brain injury: effects of acidosis and corticosteroid administration**. J Neurosurg. September 4, DOI: 10.3171/2009.8.JNS081704.

Truettner JS, Hu K, Liu CL, Dietrich WD, Hu B (2009). **Subcellular stress response and induction of molecular chaperones and folding proteins after transient global ischemia in rats**. Brain Res 1249:9-18.

Wang MY, Levi AD (In press). **Minimally invasive cervical fusion**. In Cervical Spine Surgery: Current trends and challenges, 1st Edition Eds: Mummanemi P, Kanter A, Wang M, Haid R. Quality Medical Publishing Inc, St. Louis, MO. Chapter 28.

Wang MY, Levi AD (In press). **Minimally invasive surgery to treat cervical spine trauma**. In Cervical Spine Surgery: Current trends and challenges, 1st Edition Eds: Mummanemi P, Kanter A, Wang M, Haid R. Quality Medical Publishing Inc, St. Louis, MO. Chapter 32.

Widerstrom-Noga EG, Cruz-Almeida Y, Felix ER, Adcock JP (2009). **Relationship between pain characteristics and pain adaptation type in persons with SCI**. J Rehabil Res Dev 46:43-56.

Widerstrom-Noga EG, Finnerup NB, Siddall PJ (2009). **Biopsychosocial perspective on a mechanisms-based approach to assessment and treatment of pain following spinal cord injury**. J Rehabil Res Dev 46:1-12.

Widerstrom-Noga EG (2009). **Pain: a multidimensional problem of national priority**. J Rehabil Res Dev 46:vii-vix.

Widerström-Noga EG (2009). **In Spinal Cord Injury Rehabilitation: Pain Sources and Management**. Contemporary Perspectives in Rehabilitation, Edelle Field Foote (Eds), FA Davis, Philadelphia, PA.

Widerström-Noga E, Finlayson M (In press). **Aging with a disability: Physical impairment, pain and fatigue**. Physical Medicine and Rehabilitation Clinics of North America, Elsevier.

Winslow J, Dididze M, Thomas CK (2009). **Automatic classification of motor unit potentials in surface EMG recorded from thenar muscles paralyzed by spinal cord injury**. J Neurosci Methods 185:165-177.

Yeaney NK, He M, Tang N, Malouf AT, O'Riordan MA, Lemmon V, Bearer CF (2009). **Ethanol inhibits L1 cell adhesion molecule tyrosine phosphorylation and dephosphorylation and activation of pp60(src)**. J Neurochem 110:779-790.

Ziai WC, Torbey MT, Naff NJ, Williams MA, Bullock R, Marmarou A, Tuhim S, Schmutzhard E, Pfaußler B, Hanley DF. (2009). **Frequency of sustained intracranial pressure elevation during treatment of severe intraventricular hemorrhage**. Cerebrovasc Dis. 27:403-10.





THE PROJECT

PO BOX 016960, R-48
MIAMI, FL 33101

Non-Profit
Organization
U.S. Postage
PAID
Miami, Florida
Permit 438

