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THE PROJECT

A PUBLICATION OF THE MIAMI PROJECT TO CURE PARALYSIS AND THE BUONICONTI FUND TO CURE PARALYSIS

The Miami Project To Cure Paralysis



Research Review 2008

In Memoriam

The Miami Project and the spinal cord injured community recently lost a true friend, advocate and educator when Maria Amador passed away. Those who had the privilege to know and work with her will sorely miss the way she always had a smile to give or a helping hand to lend. The tremendous impact of her contributions to the cause of curing paralysis will be felt as we continue to do what she would want us to do, move forward and gather the knowledge that will soon free those who are confined to wheelchairs.

Maria's tasks at The Miami Project were immense, daunting and often very difficult, but she never shied away from trying to fully understand the complex science at hand and expertly put it into words that everyone could understand. She served as the critical bridge from the scientific team to the support staff, spinal cord injured community and their loved ones.

"Maria had the special talent of translating our science into sentences that could be understood and appreciated by the general public. Maria will always remain in our hearts and minds as we continue to work on her lifetime goal of finding a cure for paralysis."

Some of the many roles during her 18 year tenure included Editor of both The Miami Project Annual Research Review and The Project, the official magazine of The Miami Project and The Buoniconti Fund, research subjects recruiter, creating and managing content for The Miami Project website, and coordinating The Miami Project and the Neuroscience Center visiting lectureship series. She helped in the design of the Education Center at the Lois Pope LIFE Center, an area that she was so proud of and worked in every day. At The Miami Project she met with thousands of people who asked questions and needed answers, hope and honesty as they or one of their family members tried to understand the complexities of their situation. The role she was most excited about was serving as the Project Coordinator for The Miami Project's Clinical Trials Initiative. She truly relished this role and looked forward to the process of taking our science to the FDA for approval. Scientific Director Dr. W. Dalton Dietrich put it best by saying, "Maria had the special talent of translating our science into sentences that could be understood and appreciated by the general public. Maria will always remain in our hearts and minds as we continue to work on her lifetime goal of finding a cure for paralysis."



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RESEARCH REVIEW 2008

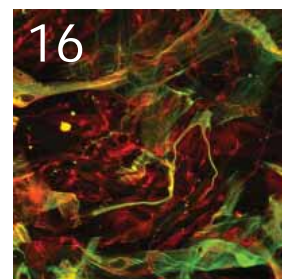
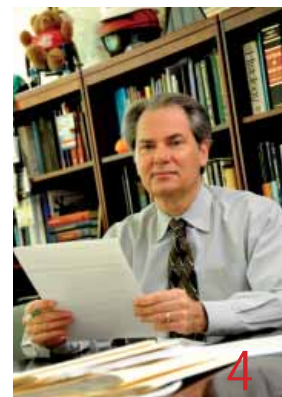
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Message From The Scientific Director

This year, Miami Project investigators have conducted studies that have changed the way we think about spinal cord injury (SCI) and how best to promote recovery of function in patients. Our scientists continue to perform critical basic and clinical neuroscience research that is uncovering vital information so we can develop new treatments to change patient's lives.

In the exciting area of axonal regeneration, we are using state-of-the-art high content screening techniques to identify new compounds that, even in the presence of inhibitory substances, promote axonal growth. We are now testing these newly identified



“hit” compounds to evaluate their effectiveness in clinically relevant models of SCI. We are also developing and testing novel bridging compounds used as conduits to encourage regenerating axons to extend across a spinal cord lesion. Our scientists with expertise in developmental neuroscience are uncovering the cellular and molecular mechanisms underlying neural cell death. They work to discover what is important for stimulating repair in adult nervous system injury.

In the area of neuroprotection, we have developed clinically relevant models of brain and spinal cord injury and are identifying previously unknown mechanisms of cell death. These new discoveries reveal new targets on which to concentrate and could lead to promising interventions for the newly injured. Cell death

is influenced by many factors so we must continue to explore how best to treat and protect against neuronal and oligodendrocyte cell death. Miami Project investigators have also identified a novel mechanism underlying the post-injury inflammation that is a component of secondary damage. Importantly, we have targeted this inflammatory process and are testing an exciting anti-inflammatory treatment that in the laboratory dramatically reduces secondary damage after both brain and spinal cord injuries. These new discoveries show promise for the development of new drugs for various neurological disorders.

In the clinic, we are now testing a new neuroprotective drug that will help deliver oxygen to protect damaged tissues. The cooling strategies developed by our scientists have already changed the way trauma patients are treated in emergency rooms and hospitals around the world.

In the area of spinal cord repair, Miami Project investigators continue to develop cellular treatment approaches that target both the acute and chronic injury state and we are testing these in both small and large animal models.

We have discussed a first-in-man clinical trial with the FDA in which we propose to use a human Schwann Cell transplantation to promote recovery in both acute and chronic SCI patients.

These studies will help position our investigators for future programs to treat patients with these types of injuries. Treatment approaches that combine cellular therapies with administration of growth-promoting factors show exciting promise as we move forward to clinical trials.

We have discussed a first-in-man clinical trial with the FDA in which we propose to use a human Schwann cell transplantation to promote recovery in both acute and chronic SCI patients. To move this clinical program forward, we are working to collect critical preclinical data required for the FDA to approve the trial. We also have other preclinical studies underway that involve the use of the drug rolipram as a neuroprotective agent. These studies are addressing questions about the dose and potential toxicity of the treatments and are necessary to move into the clinic.

Therapies to improve the overall health of a person with SCI and to improve quality of life continue to be an

important mission for our scientific investigators. Novel rehabilitation approaches that improve a person's upper extremity function as well as their walking and balance will one day be used in concert with the reparative strategies we are studying in the laboratory. New approaches that limit neuropathic pain in patients with SCI are being tested in the laboratory and clinic. We are also making continuing progress with other problems experienced by the SCI community including obesity and male infertility.

Our investigators continue to train the next generation of scientists, recruiting the "brightest and best" to our laboratories to help with this challenging problem. Miami Project scientists collaborate and publish with national and international leaders in the SCI field as we continue to move this exciting field forward.

Finally, our clinical trials initiative is a critical part of our program that puts emphasis on a smooth translation of our discoveries to patients. Several new clinical trials are underway or in various stages of development that will provide critical information for translating new treatments to

the trauma patient.

Because our research and clinical programs are multidisciplinary, we are able to attack the complex problems associated with nervous system injury from many fronts. I am grateful to lead such a dedicated and talented team of scientists and researchers.

We are truly blessed with the continuing support of many friends, individuals, foundations and government agencies.. Thank you for this support and we all look forward to an even more exciting 2009.

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

Message From The Co-founder

It is with great pride that I walk the halls of Jackson Memorial Hospital, the third largest and one of the busiest teaching hospitals that is ranked among “America’s Best.” Whether in the emergency room, the operating room or the trauma center, I can see the results of Miami Project research efforts in the patients we’ve treated. Every week, I perform surgery on potentially high risk patients with spinal cord injuries, tumors and cysts whose nervous systems are protected from damage when we use sophisticated intraoperative monitoring techniques developed by Miami Project clinical researchers in neurophysiology. You can only imagine how proud I am to have been a part of the basic science and clinical research that led to the FDA approval of this monitoring technique.



We are also now observing encouraging results with hypothermia treatment delivered through an intravascular catheter that lowers body temperature in a controlled and safe fashion. It's gratifying to know that we contributed to the evidence-based medicine that led to the American Heart Association's endorsement of hypothermia for cardiac arrest. We are now leading the important clinical investigations to substantiate the use of hypothermia for brain and spinal cord injury, a therapy we expect will be used widely someday and that paramedics in South Florida and across the U.S. are beginning to include in their delivery of emergency care.

I am grateful to and have the deepest respect for Dr. Dalton Dietrich and our Research Faculty in the basic sciences and clinical laboratories whose work is outlined in the following pages. They are putting their hearts and minds together to change the way patients are treated today and in the future, not only in our hospitals but around the world. The Miami Project's scientists and clinical researchers meet often to intensely focus on expediting the research that will lead to FDA approval for our transplantation of Schwann cells into patients with both acute and chronic spinal cord injuries. Despite the current socioeconomic challenges faced worldwide, we are able to invest heavily in this labor and cost intensive process. This is largely because of the extraordinary generosity of Miami Project donors, to whom we owe a debt of gratitude.

What a great time to be alive and to witness the renaissance of neuroscience. Legitimate treatment possibilities have been identified by Miami Project investigators and their colleagues, and as we enter 2009, significant research milestones are in sight. It's a new age of possibilities and the probability for success has never been higher.

With all of my warmest regards.

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

The Miami Project scientific team is grateful for the dedication and hard work of 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.



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CLINICAL TRIALS UPDATE

Recent Accomplishments

Completed an initial Hypothermia clinical study in 14 patients with acute spinal cord injury

Gained U.S. Department of Defense funding to support a Phase 2 Oxycyte trial

Established a Clinical Trials Unit

Organized a working team to assemble an IND (Investigational New Drug) application for a Phase 1 trial of autologous human Schwann cell transplantation

Had a pre-pre IND discussion with the FDA (Food and Drug Administration) that provided guidance for the design and implementation of FDA-required safety studies to assess the potential risks of Schwann cell transplantation prior to approval for human trial

“By establishing the Clinical Trials Unit, an infrastructure has been set in place to fuel more than just one clinical trial”

Research That's Making A Difference

Is it luck? Or are a handful of patients treated at the University of Miami/Jackson Health System Medical Center the beneficiaries of a new therapy for acute spinal cord injury; a therapy that's based on laboratory experiments done years before?

Therapeutic hypothermia has been the focus of much attention after Kevin Everett, National Football League player, experienced a remarkable recovery after his severe spinal cord injury. Mild hypothermia for patients who suffer certain types of heart attacks is becoming a standard treatment. In fact, the American Heart Association has

published guidelines for the use of hypothermia in this patient population. Could this up-and-coming therapy also ease the degree of disability for those suffering spinal cord injury?

“There’s enough information here to be excited about doing a prospective trial.”

Over the last two years, clinical scientists at The Miami Project and the Department of Neurological Surgery have examined the use of therapeutic hypothermia in 14 patients with acute cervical spinal cord injury. Their initial experience with the clinical application of modest hypothermia after spinal cord injury has been accepted for publication in an upcoming issue of the *Journal of Neurotrauma*.

Summarizing their preliminary findings, Allan Levi, M.D., Ph.D., a neurosurgeon and lead investigator, said, “I think there’s enough information here to be excited about doing a prospective trial. It looks like the treatment, if used correctly, is pretty safe.” The group has prepared another article that will undergo review by their peers and will describe the clinical results of the 10 males and 4 females who participated in the study.

So far with respect to safety, the researchers have noted a few complications, most commonly pneumonia and acute respiratory distress syndrome as well as lower heart rates. In this study, none of the participants experienced life threatening complications such as deep venous thrombosis, pulmonary embolism or myocardial infarction.

The investigators will continue evaluating the treatment’s effectiveness, and are working on overcoming a challenge with the timing of the treatment. “We would like to see a major improvement in the time between the injury and the initiation of hypothermia,” says Dr. Levi. It took an average of 9 hours to begin the hypothermia treatment and another 3 hours to reach the target body temperature. “We need to do better,” says Barth A. Green, M.D., who believes cooling is likely to be most effective if prehospital treatment protocols can be developed and tested. “We know early cooling is better,” comments W. Dalton Dietrich, Ph.D., whose findings in preclinical studies show that cooling immediately after injury improves outcomes.

For hypothermia to become a standard treatment for acute spinal cord injury, more evidence than what this preliminary study can generate will be needed. The study included just a small number of patients whose results were not compared with a control group of newly injured patients not receiving the treatment. To more clearly determine the neuroprotective benefits of hypothermia, the investigators are planning a prospective multicenter trial with a larger group of patients. Neurosurgeon Michael Wang, M.D., is currently heading an effort to move this study to the next phase. He and fellow investigators are negotiating a plan to conduct this trial with the Neurological Emergencies Treatment Trials group, a network of 17 academic medical centers with emergency personnel available to conduct large multicenter clinical trials.

The experimental use of hypothermia in people with nervous system trauma came about after years of laboratory research conducted by W. Dalton Dietrich, Ph.D., and his colleagues. Their work, beginning in the 1980s, showed that cooling the body temperature a couple of degrees resulted in improved recovery of walking in paralyzed rats. Currently, they continue their work to gain a better understanding of the biochemical, histological and physiological effects of hypothermia.

It took some years to begin testing this therapy in people partly because reliable methods to cool patients still needed to be developed. By the year 2000, several companies had developed devices to control a patient’s temperature. An initial goal of using cooling devices was to counteract fever in patients with stroke, heart attacks, head trauma and spinal cord injury. Fever is common in these patients and studies by various investigators, including Helen Bramlett, Ph.D., at The Miami Project, report that small increases in body temperature can worsen neurological outcome.

Today’s very sophisticated cooling devices now allow clinicians to accurately record and manipulate a patient’s body temperature. With this degree of control, it appears possible to safely cool injured patients and, with further study, potentially give them a chance for better neurological recovery.

Better Than Blood?

With traumatic brain injuries so prevalent in the Iraq war, the U.S. Department of Defense has agreed to fund \$1.9 million of the cost of the trials on Oxycyte at the University of Miami and Virginia Commonwealth University. Oxycyte is a perfluorocarbon-based oxygen therapeutic that has shown the ability to deliver four times more oxygen than red blood cells to damaged brain tissue.

M. Ross Bullock, M.D., Ph.D., professor of neurological surgery and director of clinical neurotrauma and principal investigator of Phase II clinical trials for the therapeutic oxygen carrier, expects to begin the trials this winter. If Oxycyte, developed by Synthetic Blood International, is successful in civilian trials, it could be used in the battlefields in a year or two. Beyond that, there are other potential uses. W. Dalton Dietrich, Ph.D., says he and other researchers will be taking a closer look at Oxycyte for use in spinal cord injury.

The Phase II trial is expected to last two years, involving 200 patients at hospitals in the U.S., including Jackson Memorial Hospital, the University of Pennsylvania, Virginia Commonwealth University, Fairfax Hospital in Virginia, and possibly hospitals in Toronto, Germany, and Switzerland.

Clinical Trials Unit

When an experimental treatment has been approved for clinical trial, it takes a dedicated and professional team of clinical trial investigators and administrators to actually carry out that trial. The Department of Neurological Surgery has developed and is supporting a Clinical Trials Unit that provides the infrastructure for the conduct of current and future clinical trials in spinal cord injury and traumatic brain injury. Co-directed by neurosurgeons Allan Levi, M.D., Ph.D., and M. Ross Bullock, M.D., Ph.D., the Unit currently includes eight neurosurgeons and two clinical research coordinators with extensive experience in Neurotrauma care. These clinicians do the “hands on” work to recruit and enroll research volunteers, administer the experimental treatment and carefully collect the clinical research data. Over the last two years, the Clinical Trials Unit has coordinated the clinical research for the hypothermia trial and is poised to conduct the Oxycyte, Cethrin, Solvay and Riluzole trials when the “green light” is given to begin enrolling volunteers.

The Clinical Trials Unit also includes administrative personnel who work behind the scenes to secure trial funding, facilitate communications with the University of Miami Institutional Review Board (IRB), and create and monitor each clinical trial budget. For the four impending drug trials, they have been responsible for negotiating with trial sponsors and have shepherded the clinical trial protocols through the UM IRB approval process.

“By establishing the Clinical Trials Unit, an infrastructure has been set in place to fuel more than just one clinical trial,” says Dr. Levi. In addition to the upcoming drug trials, the Clinical Trials Unit will be ready when the development of human Schwann cell transplants is completed and we receive FDA approval to begin that trial.



Some members of the Clinical Trials Unit: (l-r) Monclar DaSilva, Research Coordinator Kimberly Fernandez, Dr. M. Ross Bullock, Dr. Allan Levi, Research Coordinator Dr. Gizelda Casella

Working Toward Approval for a Phase 1 Clinical Trial To Test Autologous Human Schwann Cells in People with Spinal Cord Injury

The Miami Project had a pre-pre Investigational New Drug (IND) discussion with the Food and Drug Administration (FDA) and received guidance on some aspects of the preclinical safety studies that need to be completed. These studies, vital for a successful IND application, are carried out under conditions that must satisfy Good Laboratory Practice (GLP) regulations. One of the goals of these studies is to establish that human Schwann cells do not form tumors or cause other toxic effects. Another goal is to generate evidence that establishes survival time of the transplanted Schwann cells. To clearly understand the potential risks associated with Schwann cell transplantation, the FDA made it clear that the duration of the tumorigenicity study should be at least six months. Before we initiate the IND-enabling GLP studies, we need to be confident that our study specific protocols and regimen are feasible and will provide the required data. Therefore, The Miami Project is currently carrying out a feasibility study to understand how long human Schwann cells can survive when transplanted into a rat spinal cord lesion and what measures can be taken to enhance survival of the transplanted cells. This information is vital to assure the success of the large and expensive GLP safety studies that we will outsource to a Contract Research Organization.

It's a new frontier for SCI researchers as well as FDA officials with respect to a cellular transplantation for spinal cord injury. So far, only one complete IND application of this kind has ever been submitted, one in which the investigators sought approval for human embryonic stem cell transplantation. Other research groups, including The Miami Project, are undertaking the IND process to bring new treatments to clinical trial.

Reaching the goal of submitting a successful IND application takes a team with dedicated members responsible for the various aspects of the regulatory and therapy development process. The Miami Project continues to build the team that will succeed in accomplishing this goal. Those currently involved with planning and conducting the ongoing preclinical studies, and preparing all the written materials that describe and support every step of producing, administering and testing the treatment are: Basic Scientists: W. Dalton Dietrich,

Ph.D., Mary Bartlett Bunge, Ph.D., Damien Pearse, Ph.D., Patrick Wood, Ph.D., Gagani Athauda, M.D., Alex Marcillo, M.D., Roozbeh Golshani, Ph.D., Yerko Berrocal, M.D.; Physician Researchers: Allan Levi, M.D., Ph.D., James Guest, M.D., Ph.D., Diana Cardenas, M.D., MHA; Project Coordinators: Anil Lalwani, Maria Amador, Zsuzsanna Nemeth; Wallace H. Coulter Center for Translational Research. Cell Processing Facility Administrators: Norma Kenyon, M.D., Jose DeSilva, Ph.D., Aisha Khan, Elina Linetsky.

Human Schwann Cell Phase 1 Trial Development Plan (subject to change)

January - June 2009

Pre IND preparations

- Complete preclinical feasibility studies (human Schwann cell survival in nude rat, transplant procedure in minipig)
- Continue cell manufacturing development and quality assurance studies
- Finalize manufacturing and study protocols for GLP studies
- Select a Contract Research Organization and negotiate contract to complete GLP studies

July - December 2009

GLP studies and IRB submission

- Continue cell manufacturing development and quality assurance studies
- Conduct GLP pharmacology/toxicology/tumorigenicity studies (6 months)
- Address changes for preclinical and clinical protocols as recommended by FDA during pre IND meeting
- Submit clinical protocol to University of Miami Institutional Review Board

January - June 2010

IND application reports

- Compile data from GLP studies
- Conduct additional studies based on results of GLP studies
- Finalize IND application materials

July - December 2010

IND submission

- File IND
- If IND approved, begin clinical trial



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Each laboratory at The Miami Project is making significant contributions in scientific knowledge needed to improve the care and treatment for SCI. Here we summarize just a few highlights from our recently published work.

International Contributions

Miami Project investigators are serving on several international committees and advisory groups that have the goal of uniting SCI researchers to advance experimental treatments to clinical trial and improve care for SCI.

James Guest, M.D., Ph.D., contributes to the collective efforts of one organization known as SCOPE, the Spinal Cord Outcomes Partnership Endeavor. The mission of SCOPE is to enhance the development of clinical trial and practice protocols so therapies for SCI can be accurately examined in trial and adopted into practice. One of their goals is to bring representatives from industry, academia, professional societies, federal agencies, not-for-profit organizations, and the community of people living with a spinal cord injury together to develop guidelines for evaluating the most promising preclinical discoveries.

Several professional organizations, such as the American Spinal Injury Association (ASIA), the International Spinal Cord Society (ISCoS), as well as governmental agencies such as the National Institutes of Health (NIH), National Institute on Disability and Rehabilitation Research (NIDRR), the Veterans Administration (VA), and the Food and Drug Administration (FDA), have sponsored and participated in a series of meetings and workshops to discuss the advancement of clinical trials for SCI. A recent workshop sponsored by SCOPE focused on “Functional Recovery after Spinal Cord Injury: Implications of Different Spinal Injury Patterns and Distinct Therapeutic Targets on Clinical Trial Outcomes.” Among the attendees were key representatives from the FDA and members of the SCI research communities.

Dr. Guest has also contributed to *Guidelines for the Conduct of Clinical Trials for Spinal Cord Injury* as developed by the ICCP panel. This collective effort, supported by the International Campaign for Cures for spinal cord injury Paralysis (ICCP), gathered an expert international panel of researchers with extensive scientific and clinical experience in SCI and resulted in the publication of a set of four guideline papers in the Nature journal, *Spinal Cord*.

Eva Widerström-Noga, Ph.D., has been involved with another international effort, the International Spinal Cord Injury Standards and Datasets project, that is formulating a standard set of data that researchers and clinicians should collect on individuals with SCI. Collecting a common set of data and measures will help create uniform terminology by which SCI professionals worldwide can make comparisons about injuries, treatments and outcomes in different patients, centers and countries. Dr. Widerström-Noga served as the chairperson for the committee that established the minimal information that should be collected with respect to pain after SCI. This committee, that also included University of Miami/Miami Project physician researcher Diana Cardenas, M.D., published *The International Spinal Cord Injury Pain Basic Data Set* in the journal *Spinal Cord* (2008). A Core Data Set and Data Sets that pertain to bowel and bladder function have also been published and work on drafting Data Sets pertaining to other body functions, quality of life, and activity and participation is underway.



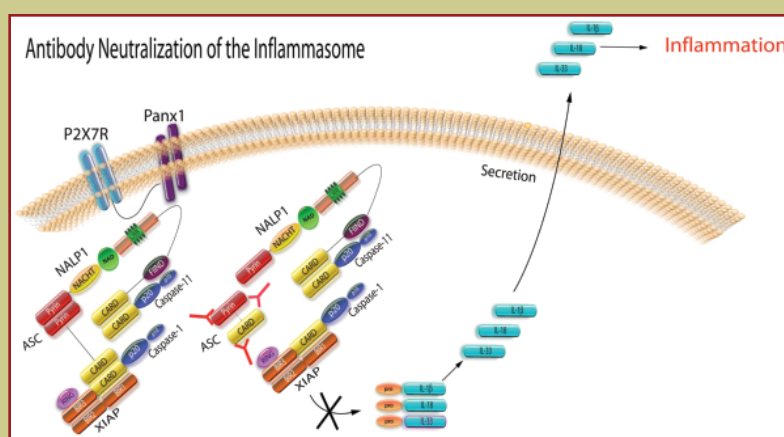


Male Fertility

Nancy Brackett, Ph.D., and colleagues have learned that poor sperm motility in men with SCI is related to the presence of inflammatory cytokines in their semen. The results of Dr. Brackett's recent studies suggest a treatment they developed and applied to a man's semen sample can neutralize the cytokines and improve sperm motility. To advance this treatment for use in fertility clinics, the investigators are conducting studies to assess whether the neutralizing treatment causes any unwanted effects. Recent results showed the treatment does not cause any damage to the sperm DNA or viability of the sperm and suggest this strategy may hold promise as a safe therapy for improving sperm motility in men with SCI.

Neuroprotection

Juan Pablo de Rivero Vaccari, Ph.D., a postdoctoral fellow and his mentors W. Dalton Dietrich, Ph.D., and Robert Keane, Ph.D., were the first to discover that neurons in the brain and spinal cord express a specific protein complex known as an inflammasome. In a study published this year, they showed that this neuronal inflammasome activates caspase 1 and other processes that lead to detrimental inflammation after central nervous system (CNS) injury. To neutralize activation of the inflammasome, they gave spinal injured rats an antibody, Anti ASC, that acts against one of the proteins within the inflammasome. In their study, they found the detrimental inflammatory cytokines and the size of the spinal cord lesion were reduced and the rats had improved motor function. These findings suggest that inhibiting inflammasome activity may offer a promising neuroprotective therapy to reduce inflammation after CNS injury and improve recovery.

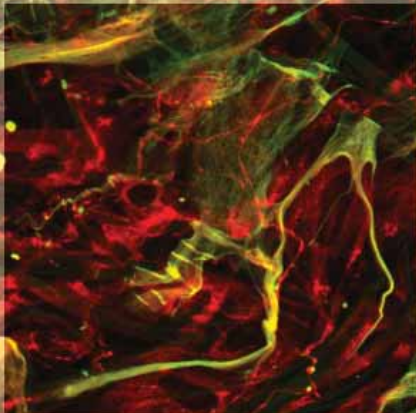


Rehabilitation

Miami Project investigators continue studies that focus on improving today's treatments and the quality of life for persons with SCI. Mark S. Nash, Ph.D., focuses his investigations on fitness enhancement as a tool to improve health and maintain function after SCI. Cardiovascular disease and related secondary complications such as obesity and cardiometabolic syndrome represent major health hazards for people with SCI and are challenging to manage once they occur. Dr. Nash's funded studies continue to provide input on the design of practical and effective exercise routines and drug therapies that counter these health risks.

Edelle Field-Fote, PT, Ph.D., studies neuroplasticity with a focus on how training combined with inputs such as stimulation and vibration enhance functional recovery after SCI. In one of her studies, she and her colleagues examined a therapy that consists of electrical stimulation of a sensory nerve in the wrist while the volunteer practices tasks with the hands. Their results indicate that sensory stimulation appears to be a valuable complement to the task practice training for improving functional use of the hands and arms in individuals with chronic SCI.

Cellular Transplantation



Miami Project investigators published several studies that further inform about the potential use of cellular transplants for spinal cord injury repair. Schwann cells, olfactory ensheathing cells and bone marrow-derived stromal cells are appealing possibilities for transplantation after SCI in humans because they are adult cells that might be harvested from a person's own body for autologous transplantation. Miami Project researchers continue to investigate ways to improve the experimental results seen with these potential treatments.

The regenerative capacity of Schwann cell (SC) implants might be improved if survival of the SCs could be enhanced. Studies by Assistant Scientist Caitlin Hill, Ph.D., and Professors Mary Bartlett Bunge, Ph.D., and Patrick Wood, Ph.D., showed that many SCs die within the first week after implantation into a contusion lesion. If they waited until 7 days after injury to transplant the cells, SC survival improved. The researchers also examined various factors present in the injury site that might contribute to the death of the transplanted cells. One substance, calpain, is associated with tissue death. When the investigators applied a calpain inhibitor to the SCs prior to transplantation, they found that the number of surviving SCs doubled.

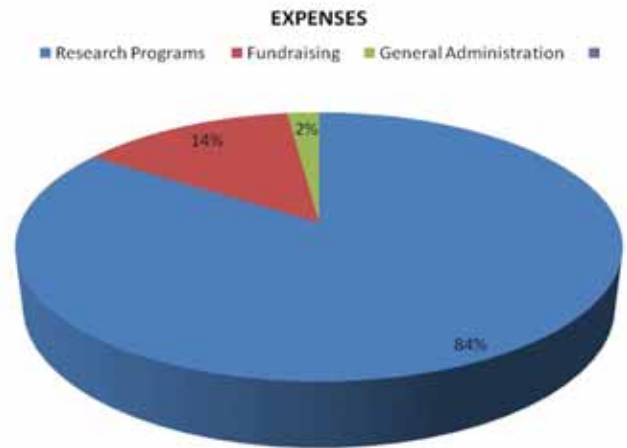
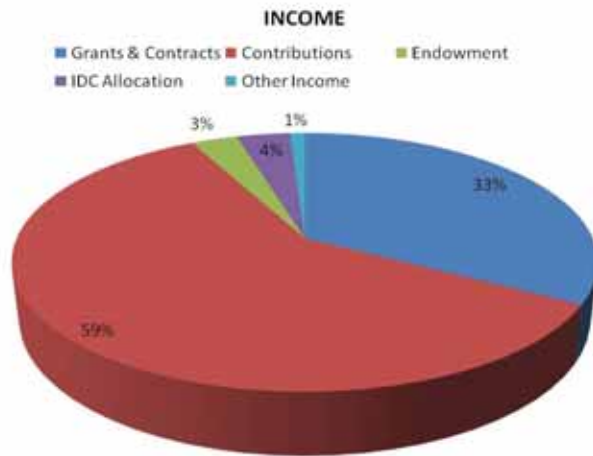
In addition to examining techniques to improve SC survival, Dr. Mary B. Bunge, her M.D., Ph.D. student Kevin Golden and other colleagues examined a strategy to enhance the length and number of axons growing within SC grafts. They used viral vector technology to transduce SCs with a molecule, D15A, that mimics the actions of two growth factors, neurotrophin-3 and brain-derived neurotrophic factor. The D15A-engineered SCs were injected into the injury center one week after a moderate thoracic adult rat spinal cord contusion. The results showed a 5-fold increase in the length of the axons, the number of SCs and the number of myelinated axons within the grafts. This treatment strategy also resulted in the highest number of regenerating axons ever observed in an experimental contusion injury site. Despite this significant regeneration, the researchers did not observe significant functional recovery in the animals. They suspect the reason may have been that the regenerating axons did not exit the graft site or that the time of testing was too short to see a functional effect.

Olfactory ensheathing cell (OEC) transplantation also has been studied as a potential repair strategy for spinal cord injury. Before pursuing clinical trials, the properties of primate OECs will need to be tested. James Guest, M.D., Ph.D., conducted a study, published this past year in *Experimental Neurology*, in which he transplanted OECs from non-human primates into rodents. He showed that primate OECs taken from the olfactory bulb can be expanded and purified in culture. To produce enough cells, however, the cell expansion procedure will likely need to be done over a longer period of time and include the use of growth promoting factors (mitogens). A positive observation made in this study was paralyzed animals treated with OECs did have smaller lesion cavities and showed superior motor recovery compared to those that did not receive OECs. Though improved motor recovery was observed, it was not directly a result of improved regeneration and connection of nerve pathways. Continued investigations will help determine whether OEC transplants are feasible for nervous system repair.

Another cell transplant option involves the use of autologous bone marrow-derived stromal (BMS) cells. BMS cells can easily be isolated from a person's own bone marrow and expanded extensively in culture. They have stem cell-like characteristics and secrete growth factors that may enhance regeneration and repair after SCI. As these cells have already been transplanted into patients in various countries, Allan Levi, M.D., Ph.D., conducted a study to determine if the cells survive, and to more clearly understand how the cells might promote functional recovery. After transplanting human BMS cells into spinal cord lesions of rodents, he found the cells do integrate into the site of injury but do not appear to become new neurons. The transplants do seem to promote axon growth, and because the size of the spinal cord lesion was reduced, the cells seem to be neuroprotective as well. With regard to cell survival, the investigators found relatively low numbers of the cells in the lesion site. They also observed no significant differences in motor function in the treated versus untreated animals. More investigations are needed to justify the use of BMS cells in humans to promote recovery after SCI.

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

Their scientific peers rate the merits of these proposed experiments and only the best receive these highly competitive awards. The government agencies listed below supported the principal investigator and the scientific project(s) indicated in fiscal year 2007-2008.



National Institute of Neurological Disorders & Stroke

Dr. W. Dalton Dietrich

- Regulation of Gliosis by Purinergic Receptor Signaling
- Facilities Of Research Excellence (For Spinal Cord Injury)
- Cyclic Nucleotide Regulation in Traumatic Brain Injury
- The Importance of Temperature on Inflammation after Traumatic Brain Injury

Dr. Jacqueline Sagen

- Neural Transplants and Spinal Neuropathic Pain Processes
- Translational Model for Novel Therapeutics in SCI Pain

Dr. Christine Thomas

- Muscle Function in Cervical Human Spinal Cord Injury
- Rescue of Denervated Muscle

Dr. John Bethea

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

Dr. Damien Pearse

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

Dr. Daniel Liebl

- Ephrins Regulate Stem Cell Proliferation following Traumatic Brain Injury

Dr. Patrick Wood

- Cytological Studies of Developing and Mature Neurons

Dr. Brian Noga

- Control of Spinal Locomotor Activity by Monoamines

National Institute of Child Health & Human Development

Dr. Edelle Field-Fote

- Improving Hand and Arm Function in Individuals with SCI-Comparison of Post-SCI Locomotor Training Techniques

Dr. Vance Lemmon

- Novel Gene Targets for CNS Axonal Regeneration

U S Army Medical Research & Material Command

Dr. W. Dalton Dietrich

- Battlefield Exercise and Combat Related Spinal Cord Injury
- 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

- Electrical Stimulation of the Midbrain to Promote Recovery from Traumatic Forebrain Injury

Florida State Department of Health

Dr. W. Dalton Dietrich

- Brain and Spinal Cord Injury Rehabilitation Trust Fund

Veteran Affairs Medical Center – Miami

- Interagency Personnel Agreements





In addition to receiving government funding, Miami Project investigators have been successful in obtaining funding from private foundations and agencies, most of which also award grants based on a peer-reviewed merit ranking. The agencies, investigators and scientific projects funded for fiscal year 2007-2008 are listed.

Biogen, Inc.

Dr. Damien Pearce
-The Use of Acute Interferon B1a Administration for Spinal Cord Injury

William Randolph Hearst Foundation Bryon Riesch Paralysis Foundation The Gordon Family Foundation

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

Craig H. Neilsen Foundation

Dr. Ian Hentall
-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

Dr. Jaqueline Sagen
-Identification and Rapid Screening of Novel Treatments for SCI Pain

Dr. Vance Lemmon
-Identification of Corticospinal Track Regeneration-Associated Genes

Christopher & Dana Reeve Foundation

Dr. Daniel Liebl
-Eph Receptors Function as Dependency Receptors Mediating Oligodendrocyte Apoptotic Cell Death following Spinal Cord Injury (Support for Fellow, Eric Runko)

Dr. Mary Bartlett Bunge
-Research Consortium on Spinal Cord Injury

Glaucoma Foundation

Dr. Barbara Grimpe
-CD44 Osteopontin Interaction in Axonal Outgrowth of Retinal Ganglion Neurons

Glaxo Smith Kline

Dr. Damien Pearce
-Promotion of Spinal Cord Injury Repair by Delivery of Anti-Myelin Associated Glycoprotein Antibodies

Infinity Pharmaceuticals, Inc.

Dr. Jacqueline Sagen
-Evaluation of Antinociceptive Compounds in Rat Models of Inflammation and Neuropathic Pain

Medtronic Sofamor Danek

Dr. W. Dalton Dietrich
-Traumatic Brain Injury Study for Medtronic

Memorial Sloan-Kettering Cancer Center

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

National Football League Charities

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

National Rehabilitation Hospital

Dr. Mark Nash & Dr. Edelle Field-Fote
-RRTC on Prevention of Secondary Conditions through Exercise: A Participatory Approach for People with 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. Daniel Liebl
-Eph Receptors are New and Novel Regulators of Cell Survival following SCI

Dr. Vance Lemmon
-Identification and Testing of Corticospinal Track Regeneration-Associated Genes

Dr. Mary Bartlett Bunge
-Development of Improved Conduits to Introduce Cells, Growth Factors and Extracellular Matrices into the Injured Rat Spinal Cord

Shriners Hospital For Children

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

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.

John Bixby, Ph.D.

Vance Lemmon, Ph.D.

Laboratory Summary: High Content Screening and Functional Genomics of the Nervous System

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 five 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 the neurons in the peripheral nervous system are able to regenerate while neurons in the central nervous system (CNS) do 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 the expression of other genes. The top TF has been confirmed to enhance neurite growth when overexpressed 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 four 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 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.

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 various 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 received an Award for Outstanding Poster at the Cambridge Healthtech Institute's High Content Analysis 2008 meeting, San Francisco, CA. He served as keynote speaker at the *ThermoFisher Bioinformatics World* conference in Las Vegas, NV, October 2008, and was an invited speaker at the *Human Genome Organization Workshop on High Content Screening* in Singapore, November 2008.

Dr. Bixby was named the Associate Dean for Graduate Studies at the University of Miami Miller School of Medicine.



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

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 received NIH funding for this line of work for a project entitled “Modulation of Hippocampal Neurogenesis and Cognitive Recovery after Neurotrauma.” This work offers the prospect of enhancing recovery in patients with residual severe neurological deficit after TBI. New drug therapies also offer the possibility of ameliorating the neuronal death that occurs in TBI. Strategies for the use of these strategies will be explored in animal models and human trials. We are particularly excited about three 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. We will further continue our investigation in a larger study. Dr. Amanpreet Singh, working as Assistant Scientist in my 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 in my lab. We are very much interested in an exciting third project in which we will isolate and culture neural progenitor cells from patients with acute brain damage. The study recently received approval from the University of Miami Institutional Review Boards and will be in full gear in the coming year. Dr. Amanpreet Singh, working as Assistant Scientist in my lab, will be leading these studies.

We have also submitted two grant applications this year to various funding agencies for studies in traumatic brain injury as well as spinal cord injury, the results of which are awaited.



Mary Bartlett Bunge, Ph.D.
Professor

Laboratory Summary: My laboratory focuses on developing combination strategies with Schwann cell implantation to repair the injured spinal cord.

Dr. Jenny Fortun has completed a project that involved increasing the level of NT-3 in the cervical region by transducing the neurons with a viral vector carrying the NT-3 gene; the viral vector was injected into the neuromuscular junction. We sought to determine whether regrowth or reorganization of corticospinal (CST) fibers could be achieved. The results showed CST fibers distal to the lesion and improvements in the rats' performance in functional tests. The importance of this study is that raising the levels of NT-3 in the cord can be done without causing injury to the spinal cord. Dr. Caitlin Hill is examining the differences in the mRNA and protein content of extending growth cones and retraction bulbs. If we understand the differences, we might then know how to treat the retraction bulbs so they would transform into a growing nerve fiber tipped by a growth cone. Dr. Eduardo Gamez fashioned a new type of gelatin channel into which Schwann cells are transplanted to bridge a complete transection in the rat thoracic spinal cord. We are evaluating nerve fiber regeneration when Schwann cells inside the channels are combined with different matrices and growth factors. Ryan Williams, a Ph.D. student, is completing his work that addresses an overall question whether axons from mature neurons in the brainstem will regenerate better onto a Schwann cell bridge when a transcription factor found in developing neurons is reexpressed. Dr. Chikato Mannoji, collaborating with the University of Florida, will evaluate the differentiation of stem and precursor cell populations in our complete transection injury paradigm. If the use of these cells appears feasible and productive, we will examine various combinatorial strategies to improve the survival and/or differentiation of these cells after transplantation.



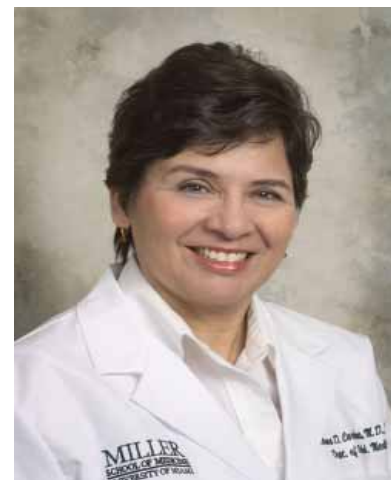
Notable accomplishments: Dr. Bunge continues as a member of the Christopher and Dana Reeve Foundation International Research Consortium and serves on the Public Education and Communication Committee for the Society for Neuroscience.

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

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:

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 patients and found that while many treatments are tried for pain in SCI, few are helpful. Many persons seek alternative medicine treatments which lead us to study self-hypnosis. Since moving to Miami in 2006, I have begun to collaborate with Eva Widerstrom-Noga, DDS, Ph.D. on studies of the underlying changes that may occur in the brain in persons with pain and SCI using Magnetic Resonance Spectroscopy.

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 has involved 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. Future studies are being planned.



W. Dalton Dietrich, Ph.D.
Professor

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.

In the first, we attempted to replicate two published manuscripts that reported the benefits of pharmacological treatments in promoting protection and recovery after SCI. These studies were supported by an NIH grant to enhance the translation of experimental findings to the bedside. Importantly, our investigative team was not successful in demonstrating treatment efficacy with either erythropoietin or minocycline. These negative findings emphasize the need for further preclinical testing before expensive clinical trials are initiated.

A second project examined the importance of a new inflammatory process in the pathophysiology of SCI. In that study, a molecular platform termed the inflammasome was identified for the first time in spinal cord neurons which activated caspase 1 and subsequent downstream inflammatory processes after SCI. Importantly, a novel treatment strategy given after the injury reduced inflammasome activation, improved motor function, and protected against histopathological damage following cervical SCI. These and ongoing studies represent a new and exciting strategy for protecting the nervous system after insults from stroke, brain trauma or SCI.

Notable accomplishments: Dr. Dietrich was named the Deputy Editor of the Journal of Neurotrauma, received a new NIH grant on the importance of hypothermia in brain injury, and was named Scientist of the Year of the Miami Chapter of Sigma Xi.



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

Laboratory Summary: My role as a researcher in the basic sciences is helping to bridge the gap in bringing exciting findings from the laboratory to the clinical arena. Most of my research involves the use of human cells, examining human spinal cord pathology, and developing clinically relevant models of neurological injuries in animals.

One clinically relevant project involves implanting FDA-approved collagen tubes filled with Schwann cells to repair lengthy gaps within the rat sciatic nerve. This preclinical work is a critical step before embarking on a clinical study that would involve placing mitogen-expanded human Schwann cells within these same tubes in patients with peripheral nerve injuries. Another of our projects, which we recently published, involved the transplantation of human bone marrow stromal cells, a type of stem cell, into the contused spinal cord of the nude rat. The goal of this study was to determine whether bone marrow stromal cells can differentiate into cells of the nervous system and if they have the potential to repair the spinal cord.



Jacqueline Sagen, Ph.D.
Professor

Laboratory Summary: Chronic pain is a frequently debilitating and poorly understood consequence of spinal cord injury (SCI). Pain due to injury to the nervous system is difficult to treat and pharmacological options for patients are marginally effective in current practice. Our laboratory continues to explore novel and more effective strategies in the therapeutic management of chronic debilitating pain.

During the past year, our laboratory has evaluated clinically available pharmacologic agents for pain-relieving potential in an SCI pain model. Drugs that block sodium channel function, such as lidocaine, have analgesic effects in patients with chronic pain due to SCI, but there are significant side-effects which limit their continual use. Recent findings in our laboratory demonstrated that ambroxol, a drug originally used in Europe to treat respiratory distress, produced robust analgesic effects in animal models of SCI pain, and this was not accompanied with the usual side-effects associated with other sodium channel blockers. Interestingly, ambroxol appeared to target particular sodium channels, such as those found in sensory neurons. The data suggest that ambroxol may be an effective and rapidly translatable analgesic drug for SCI pain with fewer side-effects than other conventional analgesic drugs.

In another study, we are exploring the use of potent peptides made by marine cone snails (conopeptides) which selectively inhibit the function of ion channels involved in the transmission of nerve signals. Among the most promising of these are MVIIA and conantokin-G (conG). Our findings showed dose-dependent analgesia following intrathecal injection of either MVIIA or conG alone, and a highly potent synergistic reduction in SCI pain using the combined peptides. These findings are particularly remarkable in light of the difficulty in obtaining even modest synergistic effects in all other drug combinations previously tested in this model and in clinical reports. While clinical use is currently limited by poor penetration to the spinal cord, peptides could be introduced via cell transplantation or gene therapy, which could provide sustained therapeutic benefits and reduce the need for repeated pain medications over the lifetime of the patients. These novel approaches will be the focus of our work in the upcoming year.



Christine K. Thomas, Ph.D.
Professor

Laboratory Summary: Our laboratory is currently asking two main questions. In our studies on people with spinal cord injury we want to understand if the involuntary contractions of paralyzed muscles (spasms) are useful to muscle health, an important consideration when voluntary control of muscle is restored. In our animal studies, we are questioning how to arrest atrophy of muscles when neurons die because of spinal cord injury, an issue we must address to rescue muscles from degeneration.

Our human studies have involved long-term (24 hr) recordings of electrical signals from various leg, arm and hand muscles. We are comparing, in injured and uninjured people, information about contraction strength, duration, frequency and the muscles that work together. The goal is to understand whether involuntary activity (spasms) can help maintain muscle strength and fatigue resistance after paralysis due to SCI.

In our studies on rats, we have tested whether adding single growth factors or combinations of factors can improve neuron survival. Only when we add particular groups of factors does neuron survival increase. More importantly, the presence of more neurons had long-term effects. The nerve supply to the muscles was restored more extensively, resulting in better muscle function.

These studies have received funding from the National Institutes of Health and the Craig Neilsen Foundation. We have presented our data at the annual Society for Neuroscience conference and at meetings that focus on plasticity of motoneurons in disease.



Pantelis Tsoulfas, M.D.
Professor

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

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. A postdoctoral fellow Mitsuhiro Enomoto carried out this work.

In the second project, we uncovered 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.



Patrick M. Wood, Ph.D.
Research Professor

Laboratory Summary: One of the major goals of transplantation research at The Miami Project is to fully explore the use of Schwann cells in cellular therapy to promote axonal regeneration and/or remyelination following spinal cord injury. Toward this goal, my laboratory is currently committed to a thorough study of the biological properties of adult-derived human Schwann cells. We have developed protocols that allow the generation, from a small biopsy of human peripheral nerve, of large numbers of Schwann cells for potential transplantation into the injured spinal cord. Efficient growth of human Schwann cells in culture requires the addition of recombinant neuregulin and the cAMP enhancer forskolin. There is evidence that exposure to these growth factors may alter the biological function of the Schwann cells and especially that long term exposure to these mitogens might increase the risk of formation of tumors following transplantation; this concern is directly relevant to regulatory approval of transplantation in clinical practice. We are now working to determine how the molecular properties of human Schwann cells change as they proliferate in culture and to determine whether any changes that do occur will affect the ability of the Schwann cells to promote regeneration or remyelination. In addition, we are studying the mechanism by which c-AMP enhancers promote proliferation. Finally, we are determining the involvement of these pathways in interactions occurring between the axons and Schwann cells.



John Bethea, Ph.D.
Associate Professor

Laboratory Summary: My laboratory has two main experimental objectives: first, to better understand how astrocytes are involved in the pathogenesis of spinal cord injury and diseases of the nervous system resulting in permanent disability such as multiple sclerosis; second, develop therapies based upon targeting host immune responses to treat spinal cord injury, multiple sclerosis and other autoimmune diseases.

In one ongoing project, we are working to better understand how a certain transcription factor, NF- κ B, regulates astrocyte injury responses. To answer this question, we generated mice lacking this pathway selectively in astrocytes. Using these mice, we recently demonstrated that inhibiting the activation of this pathway in astrocytes reduces inflammation and restores functional recovery in a mouse model of multiple sclerosis. Interestingly, we have also determined that there is a significant increase in myelin gene and protein expression as well as in the expression of regeneration associated neuronal genes. These data suggest that inhibiting NF- κ B activation in astrocytes may promote remyelination and axonal growth.

In support of this, we have recently completed a microarray study in spinal cord injured mice and have determined that inhibiting astroglial- NF- κ B significantly increases the expression of genes important in oligodendrocyte development from neuronal progenitor cells. Another project we are working on is targeting memory T cells as a therapy for multiple sclerosis and other autoimmune diseases. We have recently determined that if we interfere with a key signaling molecule required to keep these cells alive, we can restore functional recovery in mice that are paralyzed from Experimental Autoimmune Encephalomyelitis (EAE).



Edelle Field-Fote, Ph.D., P.T.
Associate Professor

Laboratory Summary: The Neuromotor Rehabilitation Research Laboratory continues to focus on using what is known about the neural control of movement, and the influence of electrophysiologic inputs, to improve function and optimize treatment strategies for individuals with spinal cord injury (SCI). This year, two exciting projects captured our excitement.

The first of these, the Whole Body Vibration Study, was a case series study demonstrating that a 12-session intervention of whole body vibration reduces spasticity and improves walking speed. This may have important implications for function and will be further investigated in a larger study. Lanitia Ness, a doctoral candidate in the Biomedical Engineering Department, was the project manager for this study. The second study, the Pediatric Locomotor Training Summer Camp study was a coordinated effort with The Miami Project, Shake-A-Leg and Ronald McDonald House wherein children came to Miami to participate in an 8-week locomotor training session and in a summer camp experience centered on accessible watersports. Kathleen Manella, a doctoral candidate in the Department of Physical Therapy was the project manager for this study.

Notable accomplishments: Dr. Field-Fote was named the new Editor-in-Chief of the Journal of Neurologic Physical Therapy. She completed her term as Chair of the NIH Musculoskeletal and Rehabilitation Sciences Study Section in June. She was honored with the 2008 Alumni Award by her Ph.D. alma mater, Washington University in St. Louis, Program in Physical Therapy.



James Guest, M.D., Ph.D.
Associate Professor

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. 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, intraoperative human spinal cord conduction studies, and research design for human clinical trials. Over the past year, we observed an encouraging degree of recovery of walking after a primate with chronic incomplete spinal cord injury was transplanted with autologous Schwann cells.

Notable accomplishments: Over the past year, Dr. Guest was appointed to the FDA's Cell and Molecular Therapeutics committee as an advisor. He was also appointed to the planning committee for the International Society for Neural Transplantation Symposia. He traveled to Argentina to evaluate centers for possible collaborations in cell therapy. Together with Dr. Steven Vanni, faculty neurosurgeon, and in cooperation with Dr. Keith Webster, Molecular and Cellular Pharmacology, he established a research program in neuroblastoma cancer stem cells. Dr. Guest serves as center principal investigator for the North American Clinical trials network.



Daniel Liebl, Ph.D.
Associate Professor

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. We also take a comprehensive approach to our experimental interests, including molecular, biochemical, genetic, cellular, behavioral, and physiological analysis. We believe a well-rounded approach is a key component of scientific studies.

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 named Director of the Neuroscience Graduate Program at the University of Miami Miller School of Medicine.



Nancy L. Brackett, Ph.D., HCLD
Research Associate Professor

Laboratory Summary: Our laboratory focuses on understanding and improving impairments to male fertility that occur following SCI. Recent studies have focused on developing a treatment modality that will solve the problem of low sperm motility in men with SCI. Treating this problem will lead to improved reproductive outcomes for couples with a male partner with SCI.

Studies in our laboratory have identified abnormal semen cytokines as major contributors to the problem. The recent work of our lab is to develop an optimal approach to neutralize elevated concentrations of cytokines in the semen of men with SCI. One approach is to neutralize the activity of individual cytokines in the semen. This will require some degree of treatment individualization, i.e., determining for each man and for each semen specimen which cytokines are abnormally elevated, and neutralizing only those cytokines. Another approach is to prevent the initial formation of abnormal cytokines in the semen. This will require identifying and then neutralizing the biochemical signals which lead to the formation of abnormally elevated cytokines in the semen.

Notable accomplishments: Dr. Brackett was named to the Editorial Board of the Journal of Andrology. She is currently President-Elect of the Society for Male Reproduction and Urology. Research from Dr. Brackett's laboratory won Best Poster Award at the 2008 American Urological Association Meeting. Dr. Brackett was selected to review P50 Center Grant Applications for the 2007 National Institute of Environmental Health and Safety DISCOVER program.



Mark S. Nash, Ph.D., FACSM
Associate Professor

Laboratory Summary: Our primary focus has been to examine causes, consequences, and treatments for early cardiometabolic diseases and related secondary complications in people with SCI. A secondary laboratory focus has been to examine fitness enhancement as a countermeasure to declining functional performance after SCI.

Exercise conditioning performed by persons without disability accelerates oxidation of body fat, and improves the lipid profile, while acute exercise speeds the clearance of post-prandial triglycerides, and reduces oxidative and inflammatory stress associated with triglycerides. When combined with well-timed protein administration, exercise conditioning also increases muscle mass and metabolism, which enhance oxidation of dietary and body fats. None of these well-established benefits have been tested in persons with tetraplegia. The Craig H. Neilsen Foundation has funded a two year study whose overarching objective is to improve fitness, reduce cardiovascular disease (CVD) risks, and enhance oxidation of dietary and body fats in persons with chronic tetraplegia through acute exercise and exercise conditioning.

The National Institute for Disability and Rehabilitation Research has funded a three-year, hypothesis-driven study to investigate effects of physical activity on obesity and obesity-related health hazards in persons with paraplegia. The study will address cardiometabolic and inflammatory vascular risks of injury, and identify an optimal exercise prescription addressing needs for endurance, strength, and anaerobic power.

Notable accomplishments: Dr. Nash served as the *Issue Editor* for an issue in Topics in Spinal Cord Injury Rehabilitation (14:3, 2009) on Cardiovascular Disease After Spinal Cord Injuries. He was appointed to the Research Advisory Board for Shriners Children's Hospitals in 2007 and the 'Carbohydrates and Lipids Clinical Practice Guideline Development Panel' of the Consortium for Spinal Cord Medicine.



Ian Hentall, Ph.D.
Research Associate Professor

Laboratory Summary: Our laboratory focuses on repairing neurotrauma by electrical stimulation in brain regions whose neurons cause widespread release of serotonin.

We recently completed a study showing that 2 brainstem regions, one in the medulla and one in the midbrain, produce a strong, permanent improvement in sensory-motor performance in rats, if they are stimulated over several days just after a moderate, incomplete, thoracic contusion injury. Also, the myelination of fibers in the spinal cord white matter and the density of serotonin-releasing fiber terminals in gray matter increases.

For traumatic brain injury, we are collaborating with Dr. Helen Bramlett in an ongoing study of rats with a moderate diffuse brain injury produced by a fluid percussion injury over the forebrain. So far, we have found that stimulation for a week in the midbrain's median raphe nucleus or dorsal raphe nucleus, beginning some hours after injury, significantly improves the rate of spatial learning in a hidden-platform swim test compared to injured, non-unstimulated rats; in fact, the rate returned roughly to that of the uninjured rat.

Notable accomplishments: Dr. Hentall has received a Department of Defense Concept Award for the collaborative study of deep brain stimulation for traumatic brain injury.



Alberto Martinez-Arizala, M.D.
Clinical Associate Professor

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 patients 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 this 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 patients care for the acutely spinal cord-injured patient and for their comprehensive rehabilitation. This setting provides a significant number of patients in which to study these disorders.



Brian Noga, Ph.D.
Research Associate Professor

Laboratory Summary: The long-term goal of our research is to develop new therapeutic strategies for enhancing spinal function by delivering neurotransmitters, similarly acting drugs, or by transplanting cells that secrete these substances. Research from many laboratories support the idea that increasing the levels of monoamine neurotransmitters can improve walking after spinal cord injury. Efforts to increase the levels of these substances following injury are limited because low concentrations are needed to avoid adverse side effects. We might overcome these limitations with the delivery of the substances to specific areas of the spinal cord where target neurons are found.

To identify potential spinal cord target areas, we have mapped the location of contacts between monoaminergic fibers (originating from the brainstem) and spinal locomotor-activated neurons. We have also demonstrated that the types of monoamine receptors known to influence locomotor activity are also found on these cells. Lastly, we have used an anatomical technique to show that monoamine-containing cells known to innervate (project to) the spinal cord are activated during walking. These results support our previous findings of spinal monoamine release during locomotion. Overall these results show that descending monoaminergic pathways are normally involved in the production of locomotion and indicate that loss of locomotor control following spinal cord injury may be due, in large part, to reduced levels of spinal monoamines. The results also indicate that monoaminergic pathways are an important target population for regeneration strategies.



Eva Widerström-Noga, Ph.D.
Research Associate Professor

Laboratory Summary: The long term goal of our research is to reduce neuropathic pain and the psychosocial impact of pain associated with SCI.

Using a mechanisms-based approach for assessing and treating this extremely difficult problem, we investigated the ability of Quantitative sensory testing (QST) to reliably characterize somatosensory dysfunction in subjects with neuropathic-like pain and SCI by measuring mechanical, vibration, and thermal detection and pain thresholds. Our preliminary evidence suggests it is a reliable adjunct measurement strategy for quantifying the neurological dysfunction associated with neuropathic pain in persons with SCI.

We have also embarked on a new study to examine the usefulness of brain imaging to evaluate clinical outcome and uncover thalamic and cortical mechanisms of difficult pain problems. Experiencing pain likely involves the activation and interaction of multiple areas of the brain. To measure metabolites in the human brain, we used a non-invasive Magnetic Resonance Spectroscopy (MRS) to assess the activity of N-acetyl aspartate (NAA) which is a free amino acid thought to be localized in neurons in the brain. NAA is a common neuronal marker that may, when its levels are decreased, be an indicator of neuronal dysfunction. Our recent findings, consistent with our previous results, indicated a neuronal dysfunction paired with glial recruitment or activation. This dysfunction may result in greater activity of excitatory neurons resulting in a heightened sensation of pain.

Notable accomplishments: Dr. Widerström-Noga served as member of the International Spinal Cord Society (ISCoS): International SCI Data set committee and chair of its subcommittee on Pain. She was also guest editor for the Journal of Rehabilitation Research & Development single topic issue on spinal cord injury-related pain.



Helen M. Bramlett, Ph.D.
Assistant Professor

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. A recent program involves developing a polytrauma brain injury model that mimics the complex conditions of blast injury in soldiers. We are using these models to develop new therapies to target both acute and chronic damage. Also, we are assessing the potentially harmful effects of general anesthesia on the aged brain as a possible mechanism underlying cognitive decline as a result of elective surgeries.

This year one of our major experimental questions related to the development of posttraumatic seizures. We have demonstrated that after trauma, seizure threshold is reduced and this results in a clinically relevant secondary injury to the brain. Importantly, it appears that posttraumatic hypothermia may reduce seizure frequency and improve outcome.

Another project involves the recently discovered phenomenon of progressive injury after brain trauma. We are utilizing a variety of strategies including Magnetic Resonance Imaging to assess the metabolic and hemodynamic status of the brain to clarify why progressive atrophy continues months to years after damage. Therapeutic interventions including anti-inflammatory and anti-apoptotic strategies are currently being evaluated.

Notable Accomplishments: Dr. Bramlett was recently appointed to the Editorial Board of the Journal of Neurotrauma. She also spoke at the Trauma Spectrum Disorders conference this year sponsored by NIH, Department of Defense and Veterans Affairs on The Importance of Gender and Race on Traumatic Brain Injury. She has accepted an additional appointment as a Research Health Scientist at the Miami Veterans Affairs.



Damien D. Pearse, Ph.D.
Assistant Professor

Laboratory Summary: In the last year, our 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 spinal cord injuries. 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 spinal cord injury, to determine if these cells enhance neuropathic pain 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 spinal cord injury by determining the best dose, route and timing of its administration to achieve maximal tissue protection. From these investigations we have found that implanting Schwann cells into the acutely or chronically injured spinal cord is not associated with an enhancement of neuropathic pain. We have also optimized the delivery of Rolipram and 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.

Notable accomplishments: Dr. Pearse received an award from the University of Chicago in 2007, the Hispanic Center of Excellence Award for Exemplary Preceptorship.



Coleen Atkins, Ph.D.
Lecturer

Laboratory Summary: Understanding the molecular mechanisms that underlie pathology in the brain after traumatic brain injury is important as we work to develop novel therapeutic interventions. During spinal cord injury, the signaling molecule cAMP is decreased and this causes inflammation in the CNS to worsen spinal cord pathology. This past year, we discovered and published the finding that cAMP levels are similarly decreased after traumatic brain injury and that raising cAMP levels with the drug rolipram decreases inflammation and improves neuronal survival in the brain after trauma.

Currently, hypothermia is perhaps the most promising therapeutic intervention for treating traumatic brain injury. This past year, we discovered and published the finding that hypothermia not only decreases pathological changes in the brain, it also stimulates and potentiates changes in the brain that improve survival of neurons. In particular, we found that hypothermia treatment increased the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and its downstream effectors, the transcription factor cAMP response element-binding protein (CREB) and the apoptotic protein Bad. Together, these findings suggest that hypothermia may improve cell survival through CREB activation and Bad inhibition.



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

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

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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.



During his visit, Dr. Hans Keirstead not only interacted with researchers but with people with SCI who attended his lecture.

September 5, 2007

Jonathan R. Wolpaw, M.D.

Wadsworth Center - New York State Department of Health
"Spinal Cord Reflex Plasticity and Motor Function in Health and Disease"

October 3, 2007

Stephen Davies, Ph.D.

University of Colorado - Denver Health Sciences Center
"Decorin and GRP-derived Astrocytes: Combination Therapies for CNS Repair"

November 14, 2007

Helen Wilshire Walsh Lecture

Hans Keirstead, Ph.D.

University of California at Irvine - Reeve-Irvine Research Center
"Spinal Cord Injury Pathogenesis and Stem Cell Strategies for Repair"

December 14, 2007

Martyn D. Goulding, Ph.D.

The Salk Institute for Biological Studies
"Genetic Dissection of Motor Circuits in the Spinal Cord"

January 9, 2008

Michael Boninger, M.D.

University of Pittsburgh School of Medicine
"Repetitive Strain of Shoulder and Wrist: What Can We Learn from Wheelchair Users"

March 5, 2008

Michael Sofroniew, Ph.D.

University of California – Los Angeles
"Recovery of Function via Relay Circuits after Spinal Cord Injury"

April 2, 2008

Mark Tuszynski, Ph.D.

University of California – San Diego
"Combinatorial Therapies for Spinal Cord Injury"

May 7, 2008

Jaynie Yang, Ph.D.

Albany Medical College
"Understanding Human Walking: From Healthy Infants to Adults with Spinal Cord Injury"

September 3, 2008

Leonardo G. Cohen, M.D.

National Institutes of Health – NINDS
"New Adjuvant Strategies to Promote Recovery of Motor Function After Stroke".

October 1, 2008

Bruce Appel, Ph.D.

Helen Wilshire Walsh Lecture

Vanderbilt University Medical Center
"In Vivo Genetic and Imaging Analysis of Glial Cell Development"

November 5, 2008

Andreas S. Beutler, M.D.

Mount Sinai Medical School – New York
"Chronic Pain: Gene Therapy to (Epi) Genomics"

December 3, 2008

Edward D. Hall, Ph.D.

Chandler Medical Center – University of Kentucky
"Newer Concepts Concerning the Role of Oxidative Damage and its Treatment in Acute Spinal Cord Injury"



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