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
2018

THE MIAMI PROJECT TO CURE PARALYSIS

UHealth UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE

Drs. Barth A. Green, W. Dalton Dietrich and Allan D. Levi

Clinical studies at The Miami Project are testing the benefits of different types of neural stimulation, including direct brain or peripheral stimulation, on spinal circuit reorganization and function.

Dear Friends and Colleagues,

The Miami Project to Cure Paralysis and our multidisciplinary research programs continue to make significant progress in basic, translational and clinical investigations. Scientific programs remain dedicated to discovering new treatments for people living with the detrimental consequences of spinal cord and brain injury. During the past year, The Miami Project and the Department of Neurological Surgery transplanted our final participant in the FDA approved Phase I trial, evaluating human Schwann cell transplantation in subacute and chronic spinal cord injured subjects. Published findings from the subacute trial showed safety, with the chronic trial expanding upon those positive results. We are now combining cell therapies with an intensive multimodal exercise and rehabilitation protocol to enhance functional outcomes and improve quality of life outcomes. In addition to SCI, the inclusion of Schwann cells with a new peripheral nerve bridging strategy has been recently approved by the FDA. This new approach to repairing traumatized peripheral nerves holds great promise in improving function and quality of life in severely injured patients.

New discoveries in other areas of neuroscience are also helping to clarify novel approaches to help protect and repair the injured nervous system. Clinical studies at The Miami Project are testing the benefits of different types of neural stimulation, including direct brain or peripheral stimulation, on spinal circuit reorganization and function. These types of investigative studies are helping to bring new technologies into the field of spinal cord injury and establishing new approaches to treat impaired motor and sensory function after SCI. For example, deep brain stimulation is currently being used by Miami Project investigators to treat neuropathic pain, which is a common consequence of SCI and important quality of life issue. The combination of biological treatments including cell therapies or growth promoting factors with state-of-the-art robotics and neuromodulation is a critical area for future research and discovery. To promote this innovative research initiative, members of our Neural Engineering Institute continue to develop new collaborations that complement our current reparative strategies and help advance new discoveries in the future. A new brain-machine interface strategy has been tested in a subject with a high cervical injury to improve upper limb function. Results thus far are encouraging and emphasize the need to combine new technologies with current therapeutic approaches to maximize success.

Our basic and translational research programs provide the knowledge required for future clinical programs as new discoveries are being made to clarify cellular and molecular mechanisms of cell death and axonal regeneration. Innovative screening strategies are identifying compounds and molecular targets that are being tested in clinically relevant models to protect injured tissues from progressive damage and promote circuit recovery. New knowledge on what factors may enhance or impede repair mechanisms after injury are also accelerating our discovery progress and identifying new therapeutics. Active collaborations with industry are also increasing our opportunities to evaluate new therapies. In addition to SCI, exciting discoveries are also being made in other models of neurological disease including traumatic brain injury, concussion, stroke, Multiple Sclerosis and Alzheimer's disease. Together these studies are providing the necessary knowledge for understanding how best to utilize combination treatments to maximize protection and recovery mechanisms after injury.

Our Educational Outreach and Training Programs continue to significantly contribute to the mission of The Miami Project. We are reaching out to individuals throughout the United States and abroad providing clinical information, resources, and news regarding progress in research and care. Over 3500 individuals living with SCI have volunteered to be in our research registry and in 2018 alone over 500 individuals participated in our active studies. A very successful Miami Project Open House was recently held that brought together scientists, consumers and family members to hear about research opportunities and answer questions. The new Christine E. Lynn Rehabilitation Institute for The Miami Project at the University of Miami and Jackson Memorial Hospital will be completed in 2020 and will allow scientists and clinicians to evaluate and recruit individuals with acute, subacute, and chronic injuries into our active clinical studies and trials.

We greatly appreciate the critical support from our friends and colleagues that are helping to move these investigations forward. We especially thank our many consumers and volunteers who participate in our clinical studies that are so very important to our mission. The Miami Project to Cure Paralysis was established in 1985 to develop new therapies to improve function in paralyzed individuals. Our scientific community is excited about the future as we conduct cutting edge research to obtain the knowledge necessary to develop and test new treatments for individuals living with spinal cord injury and other neurological disorders.

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On the cover: Image of a mouse brain at the midbrain and brainstem regions showing group of nerve cells and descending nerve fibers from the cerebral cortex that are essential for controlling voluntary movements

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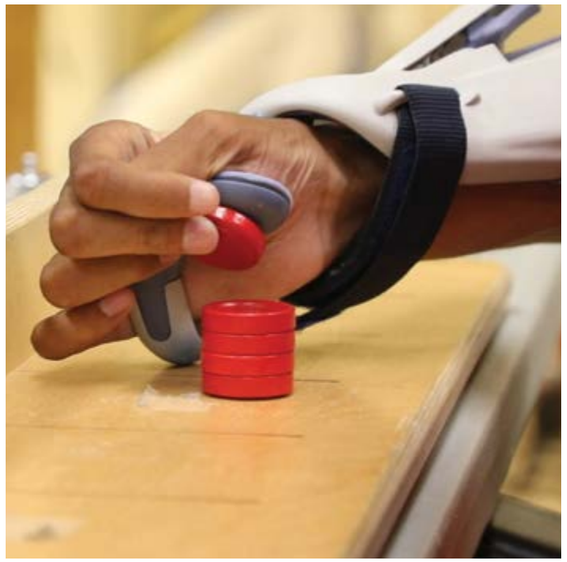
What if?

What if paralyzed limbs could move using only the power of one's thoughts?

Transforming Thoughts to Movement Offers New Hope After Spinal Cord Injury

Borrowing a story line from the realm of science fiction, a team of researchers at The Miami Project to Cure Paralysis—together with neurosurgeons and biomedical engineers from the University of Miami Miller School of Medicine—are using a brain-machine interface to make this once seemingly impossible feat a reality for people living with spinal cord injury (SCI).

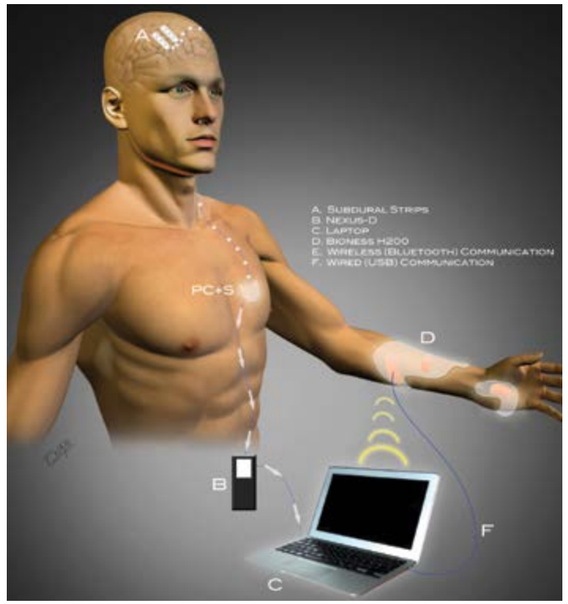


Seeking innovative ways to restore function after SCI is one of the central goals for The Miami Project, which was founded in 1985, and has grown to become an international leader in SCI research and a model for other institutions developing new scientific centers.

On November 30, 2018, neurosurgeon Jonathan R. Jagid, M.D., associate professor, neurological surgery, and Abhishek Prasad, Ph.D., assistant professor, biomedical engineering, led a surgical procedure in which an investigational system was implanted on the brain of a research participant with SCI.

The 22-year-old man sustained a SCI at the 5th cervical-level (C5) as a result of a motor vehicle accident a few years ago. He now has no movement or sensation below the elbow and requires round-the-clock nursing care for most aspects of daily living.

Despite fully paralyzed muscles, the research participant is able to stack chips using hand movements controlled by his own thoughts



Electrodes on the brain, connected to an implanted control system, communicate wirelessly to enable hand movements

Because the spinal cord carries information from the brain to the muscles, people with SCIs in the high cervical area often do not have the ability to control hand movements. Remarkably, however, the cells in the brain still respond when a person even *thinks* about moving their hand.

For SCI researchers, the challenge has been trying to read those signals from the brain and bypass the injured spinal cord to achieve movement of paralyzed muscles. In the 1970s, Jacques Vidal, Ph.D., professor emeritus, computer science at UCLA, coined the term "brain-computer interface" as he began exploring ways in which brainwaves could be used to control external devices. Research into human-machine interaction has exploded over the past few decades as scientists from around the world look at ways to use non-invasive and permanently implanted sensors to record brain activity and control everything from screen cursors to robotic arms.

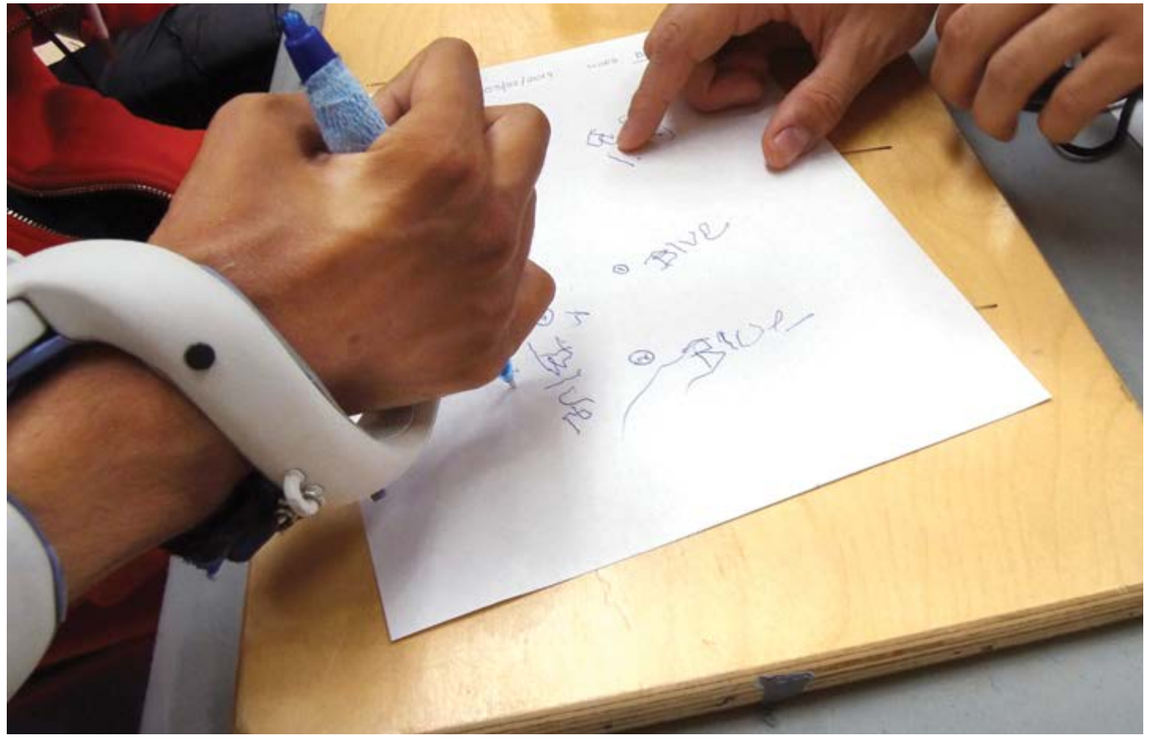
At the Miller School of Medicine, Dr. Jagid worked with Michael Ivan, M.D., assistant professor of neurological surgery and an expert in brain mapping, to stimulate different areas of the brain to identify the precise area which controls the research participant's dominant right hand. Dr. Jagid and his team then implanted the device over that particular region of his brain.

Following the surgery, the team spent weeks using a sophisticated program to "train" the computer to understand when thoughts of hand movement were observed in the electrical activity from the research participant's brain. Within milliseconds of a signal being detected, special algorithms determine whether he is thinking about moving his hand. Electrical signals are then sent to an external orthosis that stimulates the research participant's hand muscles and causes them to open or close, much the same way that his body did before injury.

With the brain-machine interface, Dr. Jagid said, the research participant is now able to successfully pick up and transport objects with his right hand.

"What is unique here is that nobody before has used this particular fully implanted device in an attempt to help a person with SCI achieve some restoration of function that can be used in a meaningful way outside of the lab setting," Dr. Jagid said. "Other devices that have achieved similar results require the person to have an implanted post protruding from the head and be tethered to a computer in a lab."

Dr. Jagid and his team hope that, in the not too distant future as technologies such as this evolve, the effect of a devastating SCI can be minimized, giving people with SCI the ability to live more independently.



Thanks to the brain-machine interface, the participant is able to write and even control a robotic walking system using signals from his brain

Joining Drs. Jagid and Prasad for this clinical trial are Iahn Cajigas, M.D., Ph.D., Resident, Department of Neurological Surgery; Noeline Prins, Ph.D., Postdoctoral Research Associate, Department of Biomedical Engineering; Michael Ivan, M.D., M.B.S., Neurosurgeon; Sebastian Gallo and Jasim Ahmad, undergraduate researchers, Department of Biomedical Engineering; Letitia Fisher, research coordinator; Anne Palermo, physical therapist; and Audrey Wilson, research associate.

In their study published in 2018, Dr. Prasad's team compared the feasibility of decoding movement information from the scalp of uninjured participants and comparing that to people who had suffered a cervical SCI. They found that despite the damage to the spinal cord, the brain signals of both uninjured subjects and SCI participants as recorded from the surface of the scalp contained sufficient information to determine when they wanted to initiate movement with high accuracy. Now with sensors sitting on the surface of the brain, the improved signal quality is already leading to better contol of the device for functional tasks.

Gant, K., Guerra, S., Zimmerman, L., Parks, B., Prins, N., & Prasad, A. (2018). EEG-controlled functional electrical stimulation for hand opening and closing in chronic complete cervical spinal cord injury. *Biomedical Physics & Engineering Express*, 4(6), 065005

Replication Studies and The Miami Project: a report from the trenches.

A report from Professor Vance Lemmon, Ph.D.

People with spinal cord injury (SCI) and their family members often ask me and my colleagues if we collaborate with scientists elsewhere and if we share our data with each other. Of course we do, that is how good science is done everywhere. On my last ten papers I have over 70 different co-authors, involving 21 institutions and 8 countries.

Liming Cheng, M.D., Ph.D., President of Tongji Hospital, Tongji University School of Medicine, Shanghai, China
Anil Lalwani, Clinical Trial Consultant, Vance Lemmon, Ph.D., Professor, Miami Project, Monica Perez, Ph.D., Professor, Miami Project, Rachel Cowan, Ph.D., Assistant Professor, Miami Project, Yan Shi, M.S., Imaging Core Manager, Miami Project, At a conference at Tongji Hospital, Shanghai, China in May, 2017

Over the past ten years or so a consensus has emerged that, before a new therapy is tested in humans with spinal cord injuries, the original animal studies should be retested to ensure the method is robust and reliable. While there are many reasons for this, the famous "Facilities of Research Excellence-Spinal Cord Injury" (FORE-SCI) program launched in 2003 by the National Institute of Neurological Disorders and Stroke (NINDS), and performed at the University of California, Irvine, the Ohio State University and the University of Miami, clearly demonstrated that many promising studies could not be replicated (PMID: 22078756). Similar lack of reproducibility in other fields has led the National Institutes of Health (NIH) and international organizations to make specific recommendations about strategies to improve the rigor of biomedical research. Chief among these are improved reporting of methods, ensuring that investigators are blinded to treatments, and that there are enough samples that the results are statistically meaningful (PMID: 20613859, PMID: 23060188). The SCI research community, including Miami Project faculty (Bixby, Bunge, Guest, Lee, Lemmon, Oudega, Park), has been at the forefront of these efforts - establishing reporting standards and data repositories (PMID: 24870067, 27055827, 28576567) and implementing best practices (PMID: 20507235, 23727091, 25902036, 28716559).

Because The Miami Project has been so successful at conducting a variety of U.S. FDA approved clinical trials, SCI researchers from around the world often reach out to us for advice about pre-clinical experiments and clinical trial design. Even me, a cell and molecular neuroscientist, gets emails and phone calls from people asking for advice. While it is true I am co-inventor on some patents about potential SCI therapeutics, our lab's work is at the beginning of the drug discovery pipeline, with little involvement in the translational efforts involving clinical trials.

In late 2016, I received an email from a professor at UCLA, Dr. Yi E. Sun. I knew her when she was a Ph.D. student at Case Western Reserve University. From there she went to Harvard where she published high impact papers on development of the brain. At UCLA, she started studying stem cells as a way to understand developmental diseases like Autism. This resulted in collaborations with a Noble Prize winner, Thomas Sudhof, at Stanford and a group of SCI scientists in Beijing. The Beijing team, led by Professor Xiaoguang Li, developed a clever biomaterial that slowly releases a growth factor that stimulates endogenous stem

I and other scientists at the conference, mindful of the poor replication track record of previous "breakthroughs", strongly recommended that an independent replication study be done prior to moving forward with clinical development of this novel combination approach.

cells in the spinal cord. The stem cells proliferate and form new neurons and glia that improve sensory and motor recovery after a large spinal cord transection in rats (PMID: 26460015, 26460053). Dr. Sun asked if I could travel to Beijing, along with other Miami Project scientists, to advise about a potential clinical trial. After reminding her that I had never been involved in a clinical trail myself, I agreed to come with colleagues to help evaluate the preclinical data and make suggestions about the feasibility of a trial.

In early February of 2017, I flew to Beijing for a kick-off meeting, along with Anil Lalwani, a biomedical engineer who had worked at the MP and been heavily involved in

Mark Tuszynski, M.D., Ph.D., Professor of Neurology, UCSD
Anil Lalwani, Clinical Trial Consultant, Stephan Züchner, M.D., Ph.D., Professor for Human Genetics and Neurology, Chair, Dr. John T. Macdonald Foundation Department of Human Genetics, Beihang University in Beijing in May, 2017

Thomas Sudhof, M.D., Ph.D., Professor Molecular & Cellular Physiology, Stanford, University. Prof. Sudhof was co-recipient of the Nobel Prize in Physiology of Medicine in 2013. Rachel Cowan, Ph.D., Assistant Professor, Miami Project. Beihang University in May, 2017

the Investigational New Drug (IND) and Investigational Device Exemption (IDE) submissions to the FDA for the Schwann cell clinical trial and medical device studies for pain. At this meeting we saw the rat data as well as unpublished data from studies in monkeys, showing that the biomaterial/growth factor combination had dramatic effects on walking. I and other scientists at the conference, mindful of the poor replication track record of previous "breakthroughs", strongly recommended that an independent replication study be done prior to moving forward with clinical development of this novel combination approach. Professor Li and his colleagues agreed, in principle, to do this. We then went to Shanghai to visit Tongji Hospital, where they were considering doing the clinical trail. This giant hospital (over 4000 beds) had a large unit set up for conducting early stage clinical research and clinical trials that complied with the Chinese FDA regulations. It also had a very busy spine surgery department that received sufficient numbers of SCI patients to conduct a meaningful phase one safety trial in a relatively short amount of time, especially compared to U.S. hospitals.

After returning to the U.S., Professor Li asked me to help organize the replication study. Since I had urged him to do this it was difficult to say no. But figuring out how to do the replication study was extremely difficult. There were at least five non-trivial problems that needed to be resolved. 1) How to fund the replication project. 2) How to overcome institutional concerns about protecting intellectual property regarding the biomaterial. 3) Deciding exactly what experiments needed to be replicated. 4) How to get it done efficiently. 5) How to not go astray of U.S. laws and regulations regarding transfer of technology to China. To deal with this last issue we got excellent training from the U.M. Export Control officer on how to comply with U.S. Department of Commerce regulations.

In May I returned with a bigger team to try to resolve these and other issues. Team members were Dr. Rachel Cowan, a Miami Project faculty member who has a spinal cord injury, Stephan Zuchner, a neurologist and chair of the UM genetics department, Yan Shi, a MP scientist who is an expert in imaging (and importantly, a native from Beijing), Monica Perez, a MP professor and expert on physical therapy and outcome measures, Anil Lalwani as a regulatory consultant and myself as a neuroscientist and the team leader. We were joined by Mark Tuszynski, a world famous SCI researcher from UCSD in La Jolla, CA. We visited the lab at Capital City Hospital where the animal work was done, looked at tissue and saw how they

When we returned to Miami, we had two different teams score the animal behavior videos in a blinded fashion. The Chinese team also scored the videos. We even had a colleague at OSU examine some of the videos to give us additional confidence.

did various experiments. We had long discussions about the experiments to be done. One big road block was that the Chinese institutions would not allow the biomaterial to leave China. Consequently, the U.S. scientists would have to come to China to conduct the experiments. Since SCI experiments take months, we agreed to come for the initiation and completion of these studies, and ensure that investigators in China were blinded by using electronic tags to identify animals that were coded by UM investigators. Prof. Tuszynski made great suggestions about how we could best do this. We then went to Shanghai to revisit Tongji Hospital and discussed details of clinical trial design. Aspects like dose and size of the implant, inclusion/exclusion criteria. Outcome measures for SCI clinical trials were discussed with the intention of planning a safe and well thought out investigation in humans – one that would satisfy SCI experts around the world as well as global regulatory authorities.

Traveling with Rachel and her wheelchair in China was an eye opening experience. From getting off an airplane, to narrow door openings in hotels, to a virtual absence of wheel chair accessible restrooms in any public buildings; being an SCI individual in China is incredibly difficult. Thank goodness for the "Americas with Disabilities Act"!

We had planned to return to Beijing in July to start the experiments but the university's animal facility was closed for complete renovation. We used this time to solve the funding problem, receiving a grant from Tongji Hospital in Shanghai, to do the experiments in Beijing and pay for the travel of the U.S. scientists. We were unable to return until the beginning of September. On this trip Prof. Dan Liebl

from the MP accompanied Yan Shi and myself to participate in all the surgeries. These were grueling days that lasted 10 hours in the surgery suite, bookended by commutes in Beijing traffic. Unfortunately, Hurricane Irma set its sights on South Florida so Dan had to rush home to take care of his family. Yan and I stayed to complete our observations of all phases of the surgeries. Only two members of the large Chinese team spoke even a little English. This was a major complicating factor, so having a Miami Project scientist, Yan Shi, on our team who was a native speaker of Chinese was essential.

In December of 2017, Martin Oudega, a member of the MP and the Principal Investigator (P.I.) on the grant form Tongji, flew to Beijing with Yan Shi and myself. Martin was the ideal P.I. He does research on biomaterials using rats and has first-hand experience with all the outcome measures the Beijing team used. We observed and videotaped the behavioral and electrophysiological tests and then observed the processing of histologic tissue and examined the specimens with confocal microscopes. These were 12 hour days in the lab for 10 straight days. Actually, the first day, we went from the airport directly to the laboratory to do behavioral testing and then went to the hotel to take a shower. By good luck, Rosario Isasi, an attorney and bioethicist and assistant professor from the U.M. genetics department was in Beijing and we took her to Beijing Changgeng Hospital, a second site being considered for a clinical trail, so we could get her advice about informed consent.

Clockwise: Chinese Spine Surgeons and the Miami team, including Ms. Shi, reviewing clinical trial procedures at Beijing Changgeng Hospital, Beijing, China; Martin Oudega, PhD, Associate Professor, Miami Project with Beihang/Capital City Hospital graduate students and staff reviewing spinal cord tissue in December of 2017; Liming Cheng, MD, PhD, President of Tongji Hospital, Shanghai, China and Vance Lemmon PhD, at a welcoming ceremony at Tongji University School of Medicine; The Beihang/Capital City Hospital surgical team with Dr. Lemmon in September, 2017

When we returned to Miami, we had two different teams score the animal behavior videos in a blinded fashion. The Chinese team also scored the videos. We even had a colleague at OSU examine some of the videos to give us additional confidence. In Miami, we examined the histological images, assembled figures and performed statistical analysis on the data. We prepared a manuscript, including a data table that reported all the results for each individual animal. When we circulated the manuscript to the co-authors, there was some back and forth about the meaning of various tests and words. But we came to consensus and Martin, as P.I., was the final arbitrator.

In the past, journals have been reluctant to publish replication studies. But the recent concerns about scientific rigor have changed everyone's mind about this. Indeed, the U.S. V.A. has recently announced a program to expressly fund replication studies. We submitted our manuscript to Experimental Neurology, an important journal in the CNS injury field and the journal that published the papers from the FORE-SCI program. The reviewers were very positive about the project and had some useful suggestions for improving the manuscript (mostly to put even more data in the appendix), which we were happy to comply with. After the paper was published (PMID: 30471251), the editor of the journal invited a German SCI researcher, Frank Bradke, to write a short commentary about it (PMID: 30605623). In the commentary, Dr. Bradke and his student, Barbara Schaffran, commented on the value of doing rigorous replications and hope our success inspires others to undertake similar replication studies to help the SCI field move forward more quickly.

In the middle of 2018, the Chinese team published their monkey results in the U.S.A. Proceedings of the National Academy of Science (PMID: 29844162). They now have a very strong package of positive results in two species along with our replication study to apply for funding for a clinical trial. If they are successful, there is a good chance they will be asking for more help from The Miami Project on next steps.

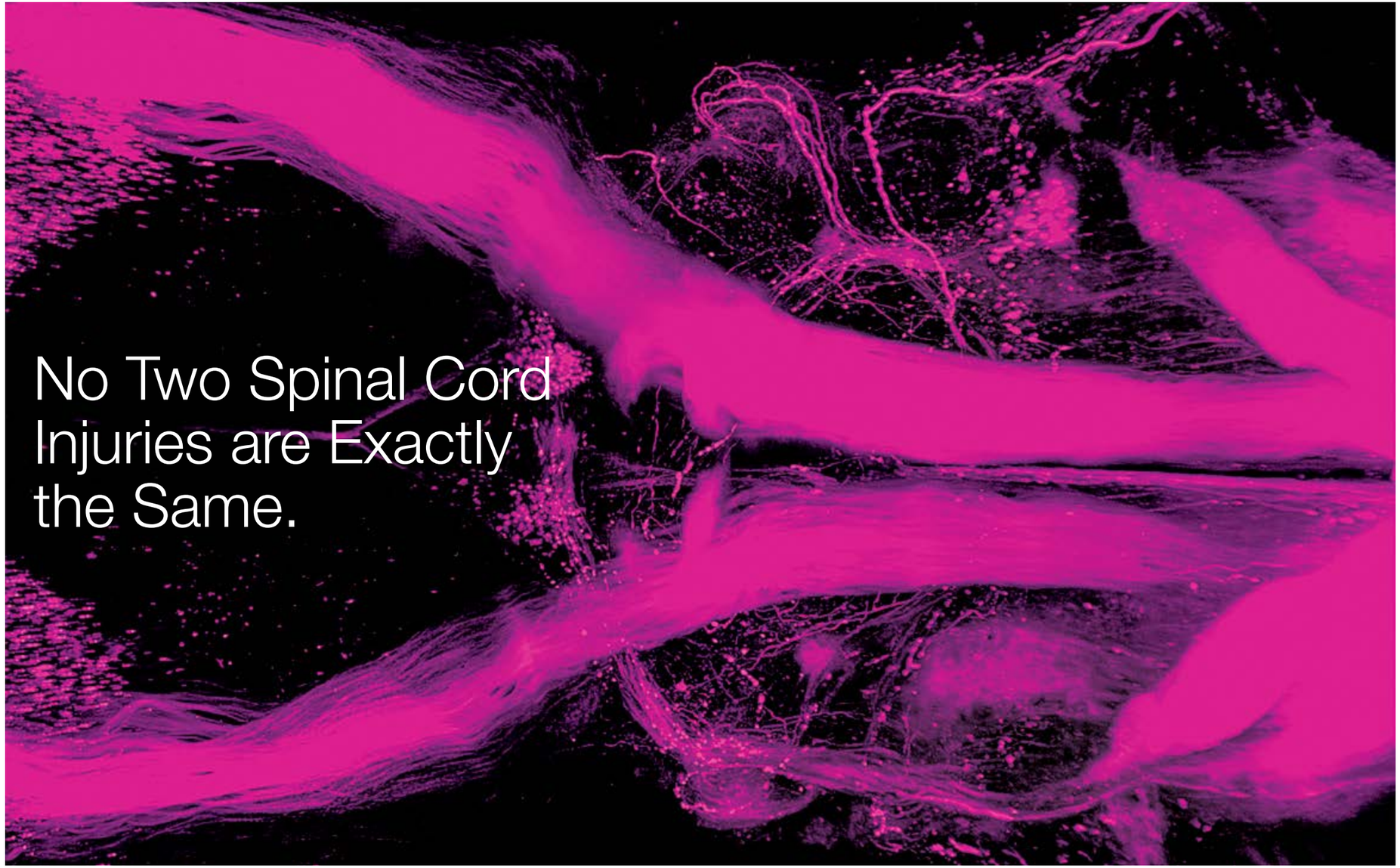


Image of a mouse brain at the midbrain and brainstem regions showing group of nerve cells and descending nerve fibers from the cerebral cortex that are essential for controlling voluntary movements

No two spinal cord injuries (SCIs) are exactly the same. Two people with the same level and grade of injury may have very different functional capabilities. In an uninjured state, the system that controls movement of the body (motor system) is incredibly complex, and countless signals from the brain, as well as the spinal cord, contribute to the generation of voluntary movements. After SCI, this system becomes even more complicated when some important structures and pathways become damaged, while others remain intact.

The inherent complexity and injury-induced variability that results from injury to the motor system can make treatment and recovery difficult. After SCI, we all know that "one size does NOT fit all." However, in this case, complexity may also afford opportunity. Widespread distribution and functional complexities within the spinal cord may actually offer an increased number of potential targets for improving function within the central nervous system. Identifying those targets is the key. Thus far, attempts to effectively map the complex network that composes the motor system have been largely incomplete. In an effort to better understand how the brain is connected to the spinal cord, scientists at The Miami Project, led by Dr. Pantelis Tsoulfas, Associate Professor, partnered with scientists from Marquette University to utilize a newly developed and powerful research tool. Retrograde viral vectors are able to move viruses along nerve fibers in the "opposite" direction, from termination of the nerve fiber (synapse) to its point of origination at the cell body (soma). They used AAV2-Retro, an adeno-associated virus that has been mutated to deliver genetic material to the cells it infects. The scientists injected AAV2-Retro into the spinal cords of rats, with and without spinal cord injuries, at different levels (cervical and lumbar). In order to visualize the neurons and their pathways, the team used special methods to "clear" the tissue, making it transparent, and highlight the areas infected by the viral vector, using fluorescent markers. Finally, 3D microscopy enabled the visualization of interconnected networks, made up of cell bodies and their projections, in the central nervous system.

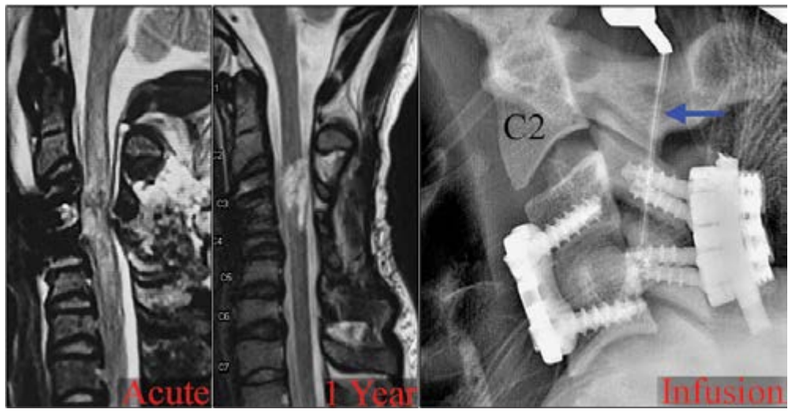
What they saw under the microscope was nothing short of amazing. The researchers were able to see intricate networks of connectivity between the spinal cord and different areas of the brain, including the brainstem, midbrain, and cortex. Within three days of injection, some important pathways, including the corticospinal tract, were clearly visible within intact tissue. Complex branching structures lit up in fluorescence and the microscopic roadmaps between the brain and the spinal cord could be appreciated in fine detail.

New and powerful research tools, like AAV2-Retro, are revolutionizing scientific discovery within the central nervous system. Researchers can now investigate what types of, and how many, neural pathways are necessary for generating voluntary movements after SCI. Retrograde viral vectors may offer an opportunity for therapeutic gene delivery to a wide distribution of neural networks involved in movement control. In turn, these targeted approaches may lead to increases in motor output and improved quality of life in people with SCI.

Wang Z, Maunze B, Wang Y, Tsoulfas P, Blackmore MG. (2018). Global Connectivity and Function of Descending Spinal Input Revealed by 3D Microscopy and Retrograde Transduction. *J Neurosci.* 5;38(49):10566-10581.

Stem Cell Trial in High-Level Tetraplegia

Within the spinal cord injury (SCI) community there is a lot of interest in cell transplantation. In some blood diseases and cancers, stem cells have shown a remarkable ability to recreate the bone marrow; for SCI, cell transplantation is more complicated and remains experimental. The original goal of transplanting "stem cells" into the injured spinal cord was to recreate lost connections and restore major functions. Given the complexity of the nervous system, this goal has not yet been achieved in people. Several cell types could potentially repair the spinal cord. Success with stem cells in other conditions has provided a basis for extensive pre-clinical studies to determine that testing in people is worthwhile. The FDA has allowed several clinical trials to explore cell transplantation after SCI in the US. The overall current results of these studies have demonstrated safety. This has been a critical step because transplanting cells directly into the spinal cord has the inherent risk of generating additional damage to fragile and delicate tissues.

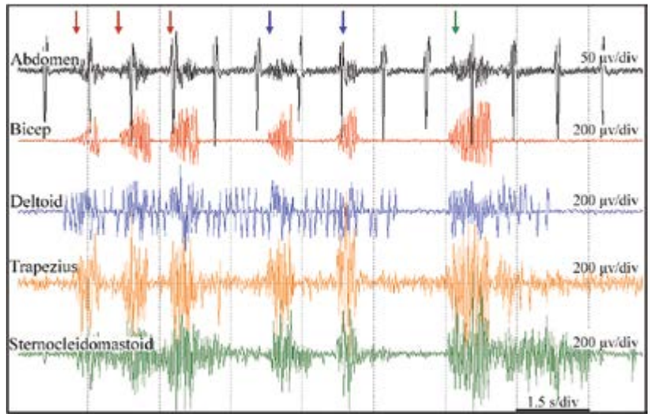


MRI of the spinal cord right after (acute) and 1 year following injury. Stem cells are infused into the spinal fluid around the cervical spinal cord

As the upper cervical spinal cord segments house critical respiratory and other homeostatic control neurons, high-level injuries are associated with the threat of losing the ability to breathe independently. For those individuals living with high-level tetraplegia, the risk that direct injection into spinal cord tissues could damage breathing circuits has limited the willingness of clinical investigators to include them in cell transplantation trials. As an alternative, there are cell transplantation strategies other than direct tissue injection such as intravenous delivery or placing the cells into the spinal fluid. These approaches rely on the ability of cells to release substances that may be beneficial by turning down inflammation, promoting cell survival, and increasing axonal growth and neuroplasticity. Delivered in these ways, the cells can act like endocrine organs that have their effects on target tissues indirectly. The intravenous and intrathecal routes of delivery may safely expand the pool of eligible participants for cell transplantation clinical trials to include people with high tetraplegia.

On a fateful day in 2014, a 25-year-old female Olympian took a life-changing fall while training on the ski slopes of Park City, Utah. She sustained a C3 level complete SCI that left her body paralyzed from the neck down, a devastating diagnosis for such a young, vibrant athlete. Her physicians in Utah reached out for guidance to Dr. Barth Green, co-founder of The Miami Project, and former Neurosurgery Chair at The University of Miami. Miami Project scientist, Dr. James Guest, Clinical Professor of Neurosurgery, an expert in SCI, in collaboration with Dr. Joshua Hare, founding director of the Interdisciplinary Stem Cell Institute, and colleagues designed and submitted to the FDA a single-patient expanded access request for the harvesting, production, and intrathecal infusion of autologous bone marrow-derived stem cells (BMSCs). The "Compassionate Use" request was based on the substantial evidence that BMSCs produce anti-inflammatory and trophic factors that could mitigate secondary damage to the spinal cord and the universal lack of other known treatments.

The young Olympian was transferred to Miami, entered rehab and was weaned from ventilator support within a month, eventually being able to breathe independently. She had immense support from her Olympic group including the team physician, physical therapist, and trainers. Together, they created a rigorous physical therapy program. Initially, she received donor cells and subsequently BMSCs cultured from her bone marrow, for a total of three infusions over one year. To increase the chance that the cells would have activity near the injury area, they were injected using radiological guidance by endovascular neurosurgeons. A small catheter was advanced inside the spinal fluid at the injury level, and the cells were slowly infused. Miami Project Scientists Drs. Andrea Santamaria and Francisco Benavides, led by Dr. Guest, assessed for changes in neurological function throughout the two-year study. This included evaluation of electrophysiological conduction of motor and sensory pathways, autonomic function, and recording of muscle electromyography activity. Additionally, researchers evaluated the injury evolution using MRI, pain assessments, bladder and pulmonary function and analyzed the participant's cerebrospinal fluid to identify biomarkers that offered further insight about the fate of the transplanted cells and the state of the spinal cord.



During deep breathing, unusual respiratory-like electrical activation of upper extremity muscles was observed

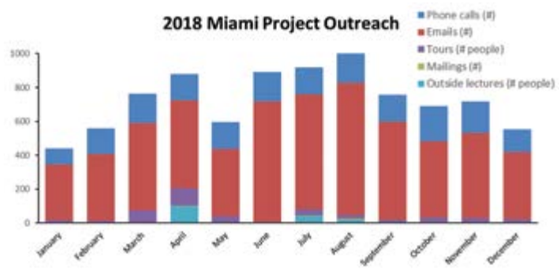
By the end of the trial, the classification of the participant's SCI changed from complete to sensory incomplete, and she recovered sensation, present but not normal, over several body regions. Importantly, no safety concerns or adverse events resulted from the procedures other than transient headache and fever after each cell delivery. Interestingly, the researchers identified some unique signal patterns during electrophysiological assessments. When the participant would take a deep breath, some muscles of her upper extremities would show "respiratory-like" electrical activation. These findings have not been previously documented in individuals with high cervical injuries and indicate that some connections between motor fibers of respiratory and upper extremity neurons were newly established or unmasked. If reproducible, this plasticity might be harnessed for a benefit in people with compromised breathing after SCI. However, further careful study is needed to understand if this occurs spontaneously, is associated with the stem cells, or another aspect of her intensive rehabilitation.

For the high-tetraplegia population, few experimental therapies are available due to concerns that there is no leeway to tolerate an adverse change. The detailed electrophysiological assessments performed at The Miami Project identified unique patterns that were not apparent through the standard clinical investigations. It is essential to mention that the medical care and rehabilitation was exceptional, aided by her long-standing athletic and psychological discipline. The participant's level of commitment to fulfill the intensive rehabilitation program and give a full effort during the clinical and experimental assessments was very inspiring for all involved. As the trial concerned a single subject, no relationship is claimed between the positive findings and the transplanted cells. The results show the feasibility of the transplant protocol and apparent lack of harmful effects. Hopefully, this study may pave the way for future cell therapeutics studies in high tetraplegia, as it sets rigorous standards for both medical care and clinical trials. This degree of caution is relevant as we explore therapeutics for the most severely injured. The combination of electrophysiology with the clinical examinations revealed significant changes that are essential at this early point in testing therapies as the effects may be small but important and undetectable by other means. This knowledge provides a basis to build and layer additional treatment approaches that may increase the potential for recovery after SCI.

OUTREACH
TO THE COMMUNITY

The Miami Project believes that an important component of developing treatments for paralysis involves communication with the community.

The Education department, directed by Katie Gant, Ph.D., is responsible for helping thousands of our community members each year. Danielle Cilien, Outreach Coordinator, and Maria Chagoyen, Education Coordinator, are the other valuable members of the team. Each year, the department answers thousands of phone calls and emails to provide people with information about all of our research programs and clinical studies, rehabilitation resources, clinical care referral, resources for living with paralysis, and advice about experimental treatments and research from around the world. We also conduct numerous tours and lectures about our research. The graph shows the total number of people interacted with each month during 2018 outreach activities.



Each month, the Education team interacts with many SCI community members to provide information about research and resources.

Volunteers in the Miami Project's research participant database continues to grow.

The Education department also assists all of The Miami Project clinical research faculty with recruitment for their clinical studies and trials. To participate in research studies individuals must first complete an intake form, which provides us with preliminary injury characteristics. Then, you receive a phone call from us to discuss the studies that you pre-qualify for and determine whether you are interested in proceeding with any studies. If so, we set up an appointment for you to come to our research center for a neurologic exam ("ASIA") and introduction to the laboratories. The graph shows the cumulative number of individuals since 2010 that have volunteered to be contacted regarding research studies for which they may qualify. If you would like to complete an intake form, please visit the following link: http://bit.ly/MP-Intake. The intake form can also be accessed from The Miami Project website, under the research participation tab. A big thank you to the on-site participants at our research center and online participants in surveys!

2018 Brain Fair at the Miami-Dade STEAM Expo.

On February 10, 2018 the Education department participated in the Miami-Dade STEAM (Science, Technology, Engineering, Art, and Mathematics) Expo as part of the Brain Fair. We hosted a spinal cord injury exhibit and provided hands-on and interactive activities to teach people of all ages about how the spinal cord interacts with the brain and controls the body. In addition to The Miami Project Education team, medical students from the Neurosurgery Interest Group (NSIG), Anelia Kassi, Justin Achua, and David Valdivia, helped teach kids about the spinal cord.

On April 21, 2018 the Education department hosted the 8th Annual Miami Project Community Open House. We enjoy this opportunity to open up our doors to the public to answer questions and share information, as well as to hear direct input from our community. The topics discussed included wound healing mechanisms after experimental SCI, cardiometabolic health and exercise in SCI, and an update on clinical trials progress. We also held a session about stem cells, including a "crash course", information about the regulation, ethics, and safety of experimental stem cell treatments, and a panel discussion with our stem cell experts. We also hosted laboratory demonstrations and tours, which included neuromotor rehabilitation, male fertility, cardiometabolic physiology, fitness and function, cells in culture, as well as our SCI Model Systems group. If you'd like to connect with our Education department, please email us at mpinfo@med.miami.edu or call us at 305-243-7108.

The 2018 Community Open House at The Miami Project included laboratory tours and demonstrations, along with scientific presentations

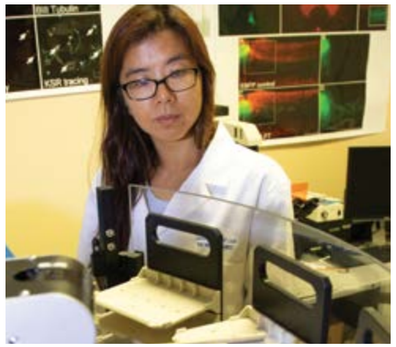
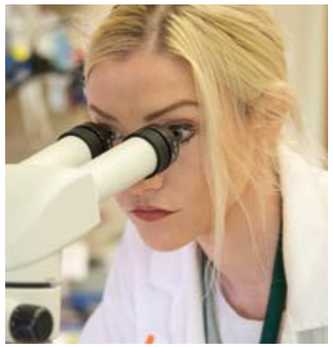
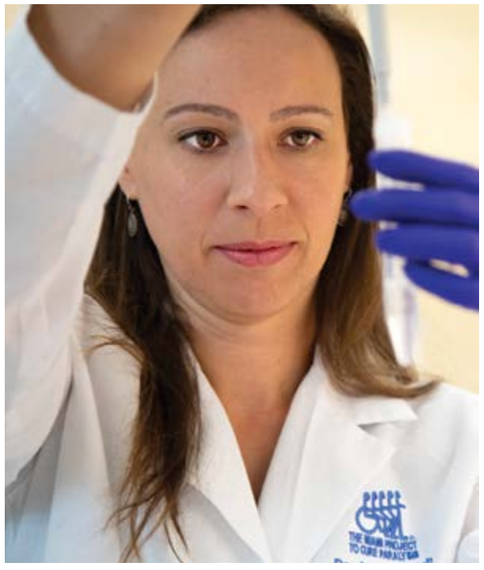
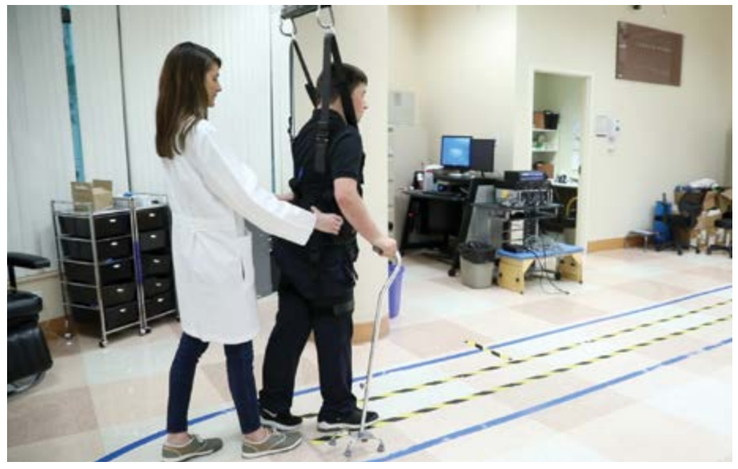
Research Funding

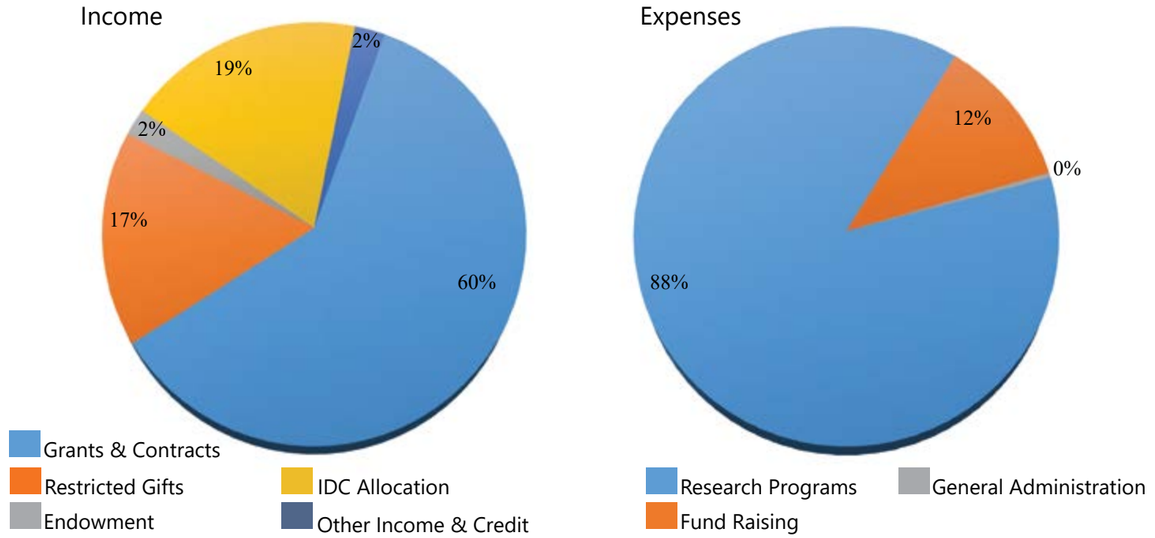
Each year, scientists at The Miami Project seek funding for their research by submitting proposals to the National Institutes of Health, the Department of Defense, and other funding agencies and foundations.

Their scientific peers rate the merits of the proposed experiments in a highly competitive process, and only the best projects are funded. The agencies and organizations listed here supported research at The Miami Project during 2018.







Brainscope II
Dr. Gillian Hotz (Site-P.I.)

Bryon Reisch Foundation
Dr. W. Dalton Dietrich, Dr. Katie Gant
-The Safety of Autologous Human Schwann Cells in Subjects with Chronic SCI Receiving Rehabilitation

Charcot-Marie-Tooth Association
Dr. Paula Monje (P.I.)
-Effect of Agents with Known Activity on PMP22 in Primary Human Schwann Cells

Christopher & Dana Reeve Foundation
Dr. James Guest (Center P.I.), Dr. Howard Levene (Co-I.)
-North American Clinical Trials Network and the Riluzole in Spinal Cord Injury Study

Conquer Paralysis Now
Dr. Mary Bartlett Bunge (Co-P.I.), Dr. Christine Schmidt (Co-P.I.)
-A New Injectable Matrix to Maximize Schwann Cell Transplantation Efficacy Following Spinal Cord Injury

Craig H. Neilsen Foundation
Dr. W. Dalton Dietrich (P.I.), Dr. Katie Gant
-Miami Project Education Program

Dr. Nancy Brackett (P.I.), Dr. Kim Anderson-Erisman (Co-I.), Dr. Charles Lynne (Co-I.), Dr. Emad Ibrahim (Co-I.)
-Management of Infertility in Men with SCI: An Educational Program for Practitioners and Clients

Dr. Catherine Craven (P.I.), Dr. Mark Nash (Co-I.), Dr. Katie Gant (Co-I.)
-Statin Monotherapy for Treatment of Endocrine Metabolic Disease Risk

Dr. James Guest (P.I.)
-Neuroprotective Effects of Internal Decompression of the Spinal Cord

Dr. Paula Monje (P.I.)
-Identity-function Definitions for Transplantable Human Schwann Cells

Dr. Mark Nash (P.I.)
-A Time-Course Study of Experimental Cardiometabolic Risk/Disease after SCI

Dr. Martin Oudega (P.I.)
-Restoring Motor Axon Circuits After Spinal Cord Injury

Dr. Monica A. Perez (P.I.)
-Corticospinal Excitability of Leg Muscles After Spinal Cord Injury

Dr. Monica A. Perez (Mentor)
-Movement Asymmetries Following Spinal Cord Injury

Danish Medical Research Council
Dr. Roberta Brambilla (P.I.), Dr. Kate Lambertsen (P.I.)
-Microglial-derived Transmembrane TNF Versus Soluble TNF: The Good and the Bad?

Department of Defense (DOD) Orthopedic Research Program of the Office of the Congressionally Directed Medical Research Programs
Dr. Jacqueline Sagen (P.I.)
-Gene Therapy for Prevention of Phantom Limb Pain Following Extremity Injuries

Department of Defense (DOD) Psychological Health and Traumatic Brain Injury Program of the Office of Congressionally Directed Medical Research Programs
Dr. M. Ross Bullock (P.I.)
-Preclinical Evaluation of FDA Approved Human Neural Stem Cells in a Rat Model of Severe Traumatic Brain Injury

Dr. W. Dalton Dietrich (P.I.), Dr. Helen Bramlett (Co-I.)
-Operation Brain Trauma Therapy Extended Studies
-The Importance of Temperature in the Pathophysiology of Mild Repetitive Brain Injury

Dr. W. Dalton Dietrich (P.I.), Dr. Helen Bramlett (Co-I.), Dr. Thomas Sick (Co-I.)

-The Use of Proneurogenic Molecules to Promote Recovery Following Acute and Chronic Traumatic Brain Injury

Dr. Eva Widerström-Noga (P.I.)
-Utility of MRS Brain Biomarkers of Pain Phenotypes after TBI

Department of Defense (DOD) Spinal Cord Injury Research Program (SCIRP) of the Office of the Congressionally Directed Medical Research Programs
Dr. Treena Arinzeh (P.I.), Dr. Mary Bartlett Bunge (Site-P.I.)
-A Combination Tissue Engineering Strategy for Schwann cell-Induced Spinal Cord Repair

Dr. Jonathan Jagid (P.I.), Dr. Eva Widerström-Noga (Co-I.), Dr. Ian Hentall (Co-I.), Dr. Alberto Martinez-Arizala (Co-I.)
-Treatment of Pain and Autonomic Dysreflexia in Spinal Cord Injury with Deep Brain Stimulation

Dr. Jae Lee (Co-P.I.), Dr. Nagi Ayad (Co-P.I.)
-Epigenetic Pathways in Spinal Cord Injury

Dr. Damien Pearse (P.I.), Dr. Howard Levene (Partner P.I.)
-Translation of Novel PDE4 Inhibitors for the Treatment of Acute Spinal Cord Injury

Dr. Shirin Shafazand (P.I.), Dr. Mark S. Nash (Co-P.I.)
-Neuro-cognitive Decline and Sleep-Disordered Breathing after SCI

Dr. Eva Widerström-Noga (P.I.), Dr. Kim Anderson-Erisman (Co-I.), Dr. Alberto Martinez-Arizala (Co-I.)
-Perspectives in Management of Severe Neuropathic Pain After a Spinal Cord Injury

Department of Defense (DOD) Spinal Cord Injury Research Program of the Office of the Congressionally Directed Medical Research Programs

Dr. Rachel Cowan (P.I.)
-Fitness and Independence after SCI: Defining Meaningful Change and Thresholds

Dr. W. Dalton Dietrich (P.I.), Dr. Michael Wang (Partner P.I.)
-Biomarkers for Spinal Cord Injury-Related Medical Complications

Dr. Allan Levi (P.I.)
-Systemic Hypothermia in Acute Cervical Spinal Cord Injury – A Prospective Case Controlled Study

Dr. Brian Noga (P.I.), Dr. James Guest (O.Q.I.), Dr. Jonathan Jagid (Co-I.)
-Gait Ignition Using DBS Following SCI

Dr. Jacqueline Sagen (P.I.)
-Developing Gene Therapies Targeting Cannabinoid Receptors for Treatment of Chronic SCI Pain

Dr. Jacqueline Sagen (P.I.)
-Engineered Neural Progenitor Transplants

in Combination with Exercise to Maximize Neuropathic Pain Reduction Following SCI

FISM Fondazione Italiana Sclerosi Multipla (Italian Multiple Sclerosis Foundation)
Dr. Roberta Brambilla (P.I.)
-Molecular Mechanisms of the Protective Function of Oligodendroglial TNFR2: A New Therapeutic Target in Neuro-Immune Disease

Florida Department of Transportation
Dr. Gillian Hotz (P.I.)
-Transportation Alternative Program: School Age Pedestrian and Bicycle Education and Injury Prevention Program in MDC

-Safe Routes to School: WalkSafe & BikeSafe Pedestrian and Bicycle Safety Program in the State of Florida

-Transportation Alternative Program

-WalkSafe/BikeSafe 5 E Model

International Spinal Research Trust
Dr. Stuart Baker, Dr. Monica A. Perez (Co-Mentors)
-Improving Grasp in Spinal Cord Injury Via a Wearable Electronic Device

Jay Weiss Institute
Dr. Hassan Al-Ali (Collaborator)
-Understanding Catchment Diversity in Personalized AML Chemotherapeutic Screening

Mazor Robotics
Dr. Michael Wang (Site P.I.)
-ADDRESS: Adult Deformity Robotic vs. Freehand Surgery to Correct Spinal Deformity

-MIS ReFRESH: Robotic vs. Freehand Minimally Invasive Spinal Surgeries

Miami Dolphins Foundation
Dr. Gillian Hotz
-MDCPSB: Countywide Concussion Injury Surveillance System

National Center for Advancing Translational Science
Dr. Hassan Al-Ali (P.I.)
-Developing a novel platform for rapid identification of drug targets and anti-targets

National Eye Institute
Dr. Ivanov Dmitri (P.I.), Dr. Kevin Park (Co-I.)
-Mechanisms of Toll-like Receptor-mediated Neurotoxicity in the Ischemic Retina

Dr. Abigail Hackam (P.I.), Dr. Kevin Park (Co-I.)
-Mechanisms of Optic Nerve Regeneration

Dr. Kevin Park (Co-P.I.), Dr. Sanjoy Bhattacharya (Co-P.I.), Dr. Vance Lemmon (Co-P.I.)
-Novel Targets to Promote RGC Axon Regeneration: Insights from Unique RGC Cohorts

National Institute of Child Health and Human Development
Dr. Vance Lemmon (Co-P.I.), Dr. John Bixby (Co-P.I.)
-Novel Gene Targets for CNS Axonal Regeneration

National Institutes of Health
Dr. Martin Oudega (P.I.)
-Mechanisms of 6-AN Facilitated Schwann Cell-Astrocyte Intermingling

National Institute of Heart, Lung and Blood
Dr. Stephan Schurer (P.I.), Dr. Vance Lemmon (Co-I.)
-Data Coordination and Integration Center for LINCS-BD2K

National Institute of Neurological Disorders & Stroke
Dr. W. Dalton Dietrich (P.I.), Dr. Katie Gant
-NIH Neurotrauma Summer Research Experience Program

Dr. Coleen Atkins (Co-P.I.), Dr. W. Dalton Dietrich (Co-P.I.)
- Cyclic Nucleotide Regulation in Traumatic Brain Injury and Alzheimer's Disease

Dr. Coleen Atkins (P.I.), Dr. Thomas Sick (Co-I.)
-Rehabilitation Strategies for Memory Dysfunction after Traumatic Brain Injury

Dr. Coleen Atkins (Co-P.I.), Dr. W. Dalton Dietrich (Co-P.I.)
-Cyclic Nucleotide Regulation in Traumatic Brain Injury

Dr. Nagi Ayad (P.I.)
-Epigenetic and Kinase Pathway Interactions in Medulloblastoma

Dr. Mary Bartlett Bunge (Co-P.I.), Dr. John Bethea (Co-P.I.), Dr. Ian Hentall (Co-I.), Dr. Paula Monje (Co-I.), Dr. Kevin Park (Co-I.), Dr. Patrick Wood (Co-I.)
-Cytological Studies of Developing and Mature Neurons

Dr. Roberta Brambilla (P.I.), Dr. Juan Pablo De Rivero Vaccari (Co-I.)
-Molecular Mechanisms of the Protective Function of Oligodendroglial TNFR2: A New Therapeutic Target in Neuro-Immune Disease

Dr. Helen Bramlett (P.I.), Dr. W. Dalton Dietrich (Co-P.I.), Dr. Daniel Liebl (Co-I.)
-A Novel Combination Strategy for Protection and Repair after TBI

Dr. W. Dalton Dietrich (P.I.), Dr. Helen Bramlett (Co-I.), Dr. Juan Pablo De Rivero Vaccari (Co-I.)
-The Importance of Temperature on the Inflammatory and Microvascular Consequences of Mild TBI

Dr. W. Dalton Dietrich (Co-P.I.), Dr. Robert Keane (Co-P.I.), Dr. Juan Pablo De Rivero Vaccari (Co-I.)
-Therapeutic Neutralization of the Inflammasome after Spinal Cord Injury

Dr. Edelle Field-Fote (P.I.), Dr. Eva Widerström-Noga (Co-I.)
-Dose-response Effects of Whole Body Vibration on Spasticity and Walking in SCI

Dr. Weiyong Gu (P.I.), Dr. Howard Levene (Co-I.)
-Modeling of Intervertebral Disc Degeneration

Dr. Gillian Hotz (Site-P.I.), Dr. Ross Bullock (Site Co-P.I.)
-Transforming Research and Clinical Knowledge in Traumatic Brain Injury

Dr. Jae Lee (P.I.)
-Targeting Lipid Clearance Pathways to Promote Repair after SCI

-Assessment of NOVO-118 as a Regenerative Therapeutic in Acute Spinal Cord Injury

Dr. Vance Lemmon (Co-P.I.), Dr. John Bixby (Co-P.I.), Dr. Jae Lee (Co-I.), Dr. Hassan Al-Ali (Co-I.)
-Targeting Multiple Kinases to Treat Experimental Spinal Cord Injury

Dr. Vance Lemmon (Co-P.I.), Dr. John Bixby (Co-P.I.), Dr. Stephan Schürer (Co-P.I.)
-Regenbase: A Searchable Database to Organize Regeneration Knowledge via Ontologies

Dr. Daniel Liebl (P.I.)
-Stabilizing the Tripartite Synaptic Complex Following TBI

-Modulating Post-Injury Gliotransmitter Levels Leads to Improved Synaptic Function (Fellowship)

Dr. Brian Noga (P.I.), Dr. James Guest (Co-P.I.), Dr. Jonathan Jagid (Co-I.)
-Gait Induction after SCI

Dr. Monica Perez (P.I.)
-Corticospinal Function after Human Spinal Cord Injury

Dr. Gaofeng Wang (P.I.), Dr. Mary Bartlett Bunge (Co-I.)
-Epigenetic Prevention of Diabetic Neuropathy by Vitamin C

National Institute on Disability, Independent Living, and Rehabilitation Research
Dr. Michael Boninger (P.I.), Dr. Kevin Dalal (Site P.I.), Dr. Rachel Cowan (Site Co-P.I.)
-Collaboration on Mobility Training

Dr. Elizabeth Felix (P.I.), Dr. Mark Nash (Co-I.), Dr. Diana Cardenas (Co-I.), Dr. Eva Widerström-Noga (Co-I.) / Dr. Rachel Cowan (Co-I.)
-South Florida Spinal Cord Injury Model Systems

Dr. Mark Nash (P.I.), Dr. Kim Anderson-Erisman (Co-I.), Dr. Rachel Cowan (Co-I.), Dr. Eva Widerström-Noga (Co-I.)
-A Lifestyle Intervention Targeting Enhanced Health and Function for Persons with Chronic SCI in Caregiver/Care-Receiver Relationships: Effects of Caregiver Co-Treatment

Dr. Zev Rymer (P.I.), Dr. Steven Kirshblum (Co-P.I.), Dr. Monica Perez (Co-P.I.), Dr. Rachel Cowan (Co-I.)
-A Multi-Center Clinical Trial to Evaluate the Effectiveness of Intermittent Hypoxia Therapy in Individuals with Spinal Cord Injury

Dr. Heather Taylor (P.I.), Dr. Eva Widerström-Noga (Co-I.)
-The Relations among Pain, Depression, and Resilience and their Prediction of Life Satisfaction in Men and Women with Spinal Cord Injury

National Multiple Sclerosis Society
Dr. Roberta Brambilla (P.I.), Dr. Hassan Al-Ali (Co-I.)
- Developing selective TNF-TNFR2 binding stabilizers to promote remyelination and repair in multiple sclerosis

New Jersey Commission on Spinal Cord Research
Dr. Ki Bum Lee (P.I.), Dr. Jae Lee (Co-I.)
-A Biodegradable Nanoscaffold for the Co-Delivery of Patient Derived Neural Stem Cells and BET Inhibitor for Anti-Inflammation and Synaptic Restoration Post-SCI

Paralyzed Veterans of America
Dr. Monica A. Perez (Mentor)
-Cortical Plasticity after Spinal Cord Injury

Pfizer, Inc.
Dr. Michael Wang (Site P.I.)
-STRIVE: Staphylococcus Vaccine Trial for Elective Spinal Surgery

Scythian Biosciences
Dr. Gillian Hotz (P.I.)
-The Effects of Cannabinoids on MTBI

State of Florida
Dr. Jacqueline Sagen (P.I.)
-Design of Inflammation-Driven Regulatable Gene Therapy for Management of Neuropathic SCI Pain

State of Florida Brain and Spinal Cord Injury Program, Department of Health, and Red Light Camera Fund
-These three state funds contribute to several research programs within The Miami Project to Cure Paralysis

State of Florida, James and Esther King Biomedical Research Program
Dr. Helen Bramlett (P.I.), Dr. W Dalton Dietrich (Co-I.)
-Whole Body Vibration Improves Stroke Outcome

Dr. W. Dalton Dietrich (P.I.)
-The Therapeutic Effect of P7C3-A20 on Stroke

The Childhood Brain Tumor Foundation
Dr. Nagi Ayad (P.I.)
-A Novel CK1δ/Brd4 Pathway for the Treatment of Medulloblastoma

UM Dean's Bridge Funding Program
Dr. Nagi Ayad (P.I.)
-Epigenetic and Kinase Pathway Interactions in Medulloblastoma

Dr. Daniel Liebl (P.I.)
-A Novel Mechanism of Cell Death in the Traumatic Injured Brain

UM Equipment Funding Program
Dr. Daniel Liebl (P.I.)
-Stabilizing the Tripartite Synaptic Complex Following TBI

UM Scientific Advisory Council Award
Dr. Kevin K. Park (Co-P.I.), Dr. Hassan Al-Ali (Co-P.I.)
-In Vivo Screening to Identify Neuroprotective Compounds for Treating Optic Neuropathy

Veterans Administration Rehabilitation Research and Development
Dr. Christopher Cardozo (P.I.), Dr. Helen Bramlett (Co-I.)
-Role of Ryanodine Receptor Dysfunction

Dr. Mousumi Ghosh (P.I.), Dr. Damien Pearse (Co-P.I.), Dr. Jacqueline Sagen (Co-P.I.)
-Modulating Microglial Phenotype to Prevent SCI-induced Central Neuropathic Pain

Dr. Michael Norenberg (P.I.), Dr. Helen Bramlett (Co-I.)
-Chronic Traumatic Encephalopathy: Role of Astrocytes

Dr. Martin Oudega (P.I.), Dr. Monica Perez (P.I.)
-Maximizing Spike Timing-Dependent Plasticity after Spinal Cord Injury

Dr. Damien Pearse (P.I.), Dr. Mousumi Ghosh (Co-I.)
-Enhancing the Reparative Efficacy of Schwann Cells Following Chronic SCI

Dr. Monica A. Perez (P.I.)
-Enhancement of Hand Motor Function after Cervical Spinal Cord Injury

Dr. Monica A. Perez (P.I.)
-Grasping Function after Spinal Cord Injury

Dr. Weiping Qin (P.I.), Dr. Helen Bramlett (Co-I.)
-Novel Pharmacological and Non-pharmacological Interventions for Bone Loss in SCI

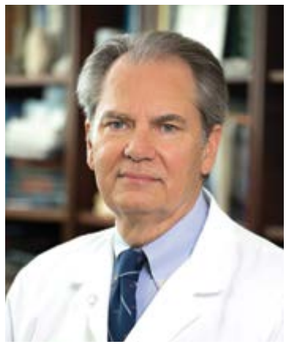
Vivian L. Smith Foundation for Neurologic Research
Dr. Jonathan Jagid (Site-P.I.)
-Hypothermia for Patients requiring Evacuation of Subdural Hematoma (HOPES) Trial

Wallace H. Coulter Foundation
Dr. Hassan Al-Ali (P.I.), Dr. John L. Bixby (Co-I.), Dr. Vance P. Lemmon (Co-I.)
-Developing a Multi-Target Small-Molecule Drug for Treating CNS Injuries

The Miami Project To Cure Paralysis

Faculty

The faculty of The Miami Project are a talented multidisciplinary team. In the following Profiles, each faculty member describes their specific research focus and highlights of recent progress.



W. DALTON DIETRICH, PH.D.

Scientific Director
Kinetic Concepts Distinguished Chair in Neurosurgery
Senior Associate Dean for Discovery Science
Co-Director, Institute for Neural Engineering
Professor, Departments of Neurological Surgery, Neurology, Biomedical, Engineering, and Cell Biology

Neuroprotection and Improved Recovery of Function following CNS Trauma

My research interest is the pathobiology and treatment of CNS injury in both the acute and chronic setting. Animal models of spinal cord injury, traumatic brain injury, and stroke are utilized to investigate the cellular and molecular mechanisms of tissue injury. The ultimate goal is to target secondary injury processes for various interventions that may protect vulnerable cell types or promote reparative processes to enhance neuroprotection, circuit plasticity, and recovery of function. The use of therapeutic hypothermia and targeted temperature management in preclinical and clinical settings is currently a focus of discovery and clinical investigations in the laboratory.

ALLAN D. LEVI, M.D., PH.D., F.A.C.S.

Robert. Buck Distinguished Chair in Neurological Surgery
Professor, Departments of Neurological Surgery, Orthopedics, and Physical Medicine & Rehabilitation
Chairman, Department of Neurological Surgery
Chief of Neurosurgery, Jackson Memorial Hospital

Cellular Transplantation Strategies after SCI/Systemic Hypothermia after Acute SCI

My clinical research interests currently focus on developing cellular transplantation strategies to repair injuries within both the human central and peripheral nervous system. I am currently Co-PI on our clinical trial "Transplantation of Autologous Human Schwann Cells (SCs) to Repair the Injured Spinal Cord - Phase I - safety study". This represents a first-in-man dose escalation study of autologous human SCs for patients with sub-acute thoracic SCI (T3 to T11). We are also very interested in the use of SCs for peripheral nerve injuries with long segmental defects and have performed such transplantations in patients with acute sciatic nerve injuries. Hypothermia continues to show promise in a variety of acute central nervous system injuries. There are various factors that need to be considered with systemic cooling of the SCI patient, including methods of cooling, window from injury to initiation, duration and depth of hypothermia, rate of re-warming, etc. While profound levels of hypothermia (T <32°C) can be difficult to administer and are subject to increased complication rates, mild (modest) levels of hypothermia (T 32-34°C) have been shown to provide significant protection against traumatic and ischemic neuronal cell death. I am currently the PI of our institutional protocol as well as a multi-center Department of Defense funded randomized trial studying systemic hypothermia induced via an intravascular catheter and continued for 48 hours after acute cervical SCI.

BARTH A. GREEN, M.D., F.A.C.S.

Professor of Neurological Surgery, Neurology, Orthopaedics, and Rehabilitation
Co-Founder and Chairman, The Miami Project to Cure Paralysis
Executive Dean of Global Health and Community Service
Ralph C. Wilson, Jr. Chair in Neurological Surgery

Translational Interventions

Over the recent years my research efforts have mainly involved taking the cutting edge basic neuroscience work product and data created by our Miami Project team from the bench to our UM affiliated clinics and hospitals. A good example of such translational research efforts has included the use of modest hypothermia for neuroprotection both in cases of acute spinal cord injury and for use in the operating room for patients undergoing high risk spinal cord surgery. I am also privileged to be able to collaborate with The Miami Project cellular transplantation programs and have been working on projects involving adult mesenchymal stem cells as well as being part of the major effort transforming our successful Schwann cell laboratory model into clinical trials. Other areas of research and clinical interest include the diagnosis and treatment of tethered cord syndrome, spinal cord cysts and Chiari I malformation.

MARY BARTLETT BUNGE, PH.D.

Professor Emerita, Departments of Cell Biology and Neurological Surgery

Development of Combination Strategies with Schwann Cells to Repair the Injured Spinal Cord

The goal in my laboratory has been to foster regeneration of axons across and beyond a spinal cord injury (SCI). To improve regeneration of axons, we have investigated the administration of neurotrophins to implants improving the survival of transplanted Schwann cells (SCs) and genetically engineering them before transplantation to improve their growth factor-secretion capability and testing matrices and conduits (in which the SCs are transplanted) for efficacy after injury. We pay particular attention to the interfaces between the SC implant and the host spinal cord to enable the ability of axons regenerated to cross them.

JOHN BIXBY, PH.D.

Professor, Departments of Molecular & Cellular Pharmacology and Neurological Surgery, Center for Computational Science, Hussmann Institute for Human Genomics, Sylvester Cancer Center
Vice Provost for Research

VANCE LEMMON, PH.D.

Walter G. Ross Distinguished Chair in Developmental Neuroscience
Professor, Department of Neurological Surgery, Center for Computational Science, Hussmann Institute for Human Genomics, Sylvester Cancer Center

High Content Screening and Functional Genomics of the Nervous System

Our laboratory has developed methods to test thousands of genes or chemicals in hundreds of thousands of neurons each week to obtain quantitative information about cell morphology and gene expression. This "high throughput" capability allows us to tackle questions about axon growth and regeneration using systems biology approaches, and to take them into animal models of injury. The Lemmon-Bixby lab has several ongoing projects related to axon regeneration. One project is to test the roles of known signaling proteins called protein kinases. In this screen we have tested >1600 kinase inhibitors, many of which strongly promote neurite growth in vitro. Using bioinformatics, biochemistry, and machine learning we can identify critical kinases and their signaling networks as well as potential lead therapeutic compounds, one of which has proven active in two different models of spinal cord injury. A second project is based on the observation that injured

peripheral sensory neurons initiate a genetic program appropriate for axonal regeneration. Our laboratory has combined next-generation sequencing with cell-based phenotypic screening to identify genes, especially transcription factors, and microRNAs that appear to regulate this genetic program, and is testing them in vitro and in vivo. Finally, in collaboration with Dr. S. Schürer, Dr. Ubbo Visser, and Drs. Nigam Shah and Alison Callahan (Stanford), we are developing RegenBase, an information system that includes an online tool for annotation of data and metadata, a knowledge base of diverse data on nerve regeneration, and an ontology that allows structured queries of the database.

HELEN M. BRAMLETT, PH.D.

Professor, Departments of Neurological Surgery and Psychology, Undergraduate Neuroscience Program Director, and Health Scientist Veterans Affairs

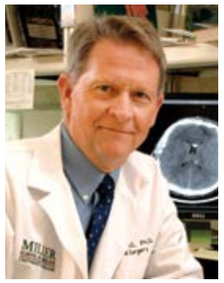
The Pathophysiology and Treatment of CNS Injury

The focus of my neurotrauma laboratory is to investigate both acute and long-term consequences of brain and spinal cord trauma. My current research interests are on the pathophysiology of traumatic brain and spinal cord injury with an emphasis on the pathogenesis of progressive white matter damage as well as the benefits of therapeutic hypothermia. My laboratory is also investigating mechanistic events leading to the development of posttraumatic epilepsy. Additionally, our current work is also focusing on complex traumatic brain injury models that mimic polytrauma as this type of injury has become more prevalent in combat areas.

M. ROSS BULLOCK, M.D., PH.D.

Professor, Department of Neurological Surgery

Director, Clinical Neurotrauma



Preclinical Mechanistic and Neuroprotection Research in Traumatic Brain Injury and Clinical Trials, and Neuromonitoring Techniques in the Injured Brain

We recently completed an extensive series of studies funded by the Department of Defense (DoD) to evaluate the neuroprotective effect of Perfluorocarbons in four rodent models of traumatic brain injury (penetrating brain injury, closed traumatic brain injury with secondary hypoxia, tissue culture with stretch injury, and mechanistic and safety studies). These oxygen carriers have shown benefit in previous studies involving fluid percussion injury and subdural hematoma models. Unfortunately, we could not demonstrate efficacy with 3 of the PFCs tested. We are also evaluating hypothermia neuroprotection, in humans and animals, using novel biomarkers. We are currently funded by the DoD to obtain efficacy and safety data with FDA approved human stem cells, transplanted into the rat brain, as therapy for penetrating TBI.

ROBERT W. KEANE, PH.D.

Professor, Departments of Physiology & Biophysics, and Neurological Surgery

Regulation of Innate Immunity after CNS Trauma

Innate immunity is the first line of defense against pathogens and host-derived signals of cellular stress. My research focuses on investigating mechanisms that direct normal innate immunity and its dysregulation in central nervous system injury and disease, including (1) agonists and activation mechanisms of inflammasomes, (2) regulatory mechanisms that potentiate or limit inflammasome activation after injury, and (3) emerging data linking inflammasome proteins as biomarkers for CNS injury.

DANIEL J. LIEBL, PH.D.

Professor, Department of Neurological Surgery

Molecular Mechanisms that Regulate Cellular Dysfunction and Death Following CNS Injury, and Mechanisms to Promote Regeneration and Recovery

The goal of my laboratory is to identify the mechanisms that lead to CNS pathophysiology and its regenerative potential. We focus on growth and guidance molecules, which play important roles in the developing, regenerating, and injured nervous systems. Specifically, we are currently interested in areas of adult neurogenesis, neuroprotection, apoptotic cell death, synaptic plasticity, angiogenesis, regeneration, and therapeutic strategies. Overall, our approach is to develop novel strategies to minimize CNS damage and maximize regeneration/tissue repair, which can be best achieved through a comprehensive mechanistic approach.

MARK S. NASH, PH.D., F.A.C.S.M.

Professor, Departments of Neurological Surgery, Physical Medicine & Rehabilitation, Physical Therapy, and Kinesiology & Sports Sciences

Physiological Assessment of Secondary Complications following SCI: Electrical Stimulation, Cardiometabolic and Vascular Physiology, Cardioendocrine Pathology and Intervention, and Exercise and Nutritional Biochemistry

One of the enduring goals of The Miami Project has been to test and then translate strategies that optimize health of persons with SCI. A significant target for this strategy has focused on physical activity to lessen secondary risks of SCI associated with physical deconditioning. We also examine complementary themes to optimize exercise prescription after SCI, identify optimal nutritional intake, and use prescription and non-prescription agents that reduce hazards of fasting and postprandial lipid disorders, dysglycemia, and vascular inflammatory stress.

DAMIEN D. PEARSE, PH.D.

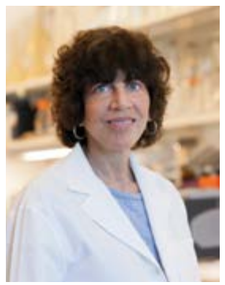
John M. and Jocelyn H.K. Watkins Distinguished Chair in Cell Therapies

Professor, Department of Neurological Surgery, Health Scientist Veterans Affairs

Exploration and Translation of Therapeutic Strategies to Repair the Injured Spinal Cord and Brain My laboratory focuses on several key aspects of CNS injury repair, including (1) the utility and clinical translation 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.

JACQUELINE SAGEN, PH.D., M.B.A.

Professor, Department of Neurological Surgery



Cellular Implants and Gene Therapy for the Alleviation of Chronic Pain and CNS Injury

Our laboratory is exploring 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 and peripheral neuropathic pain 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.

THOMAS J. SICK, PH.D.

Professor of Neurology and Physiology/Biophysics

Cellular and Neuronal Circuit Alterations after Traumatic Brian Injury That Contribute to Cognitive Decline and Epilepsy

My laboratory is conducting electrophysiological assessments of neuron and brain circuit alterations that occur after traumatic brain injury. Long-term clinical consequences of brain injury include declines in cognitive function and in many cases the development of epilepsy. We are trying to understand how circuits in the brain change over time after injury and how these changes might lead to alterations of brain function and behavior.

MICHAEL Y. WANG, M.D., F.A.C.S.

Professor, Departments of Neurological Surgery and Physical Medicine & Rehabilitation

Director of Neurosurgery, University of Miami Hospital

Spinal Cord Injury Outcomes

My primary research has been in the investigation of SCI Outcomes. I work with Miami Project researchers Drs. Allan Levi and Barth Green in studying the clinical effects of hypothermia. Currently, a multi-center randomized, prospective study on the effects of hypothermia in SCI is ongoing. In addition, I am studying the clinical application of SCI biomarkers to predict the effects of both injuries as well as therapeutic interventions with Drs. Dalton Dietrich and Ross Bullock.

KIM ANDERSON-ERISMAN, PH.D.

Research Professor, Department of Neurological Surgery (until March 1, 2018)

Director of Education, The Miami Project to Cure Paralysis (until March 1, 2018)

Translational Investigations for Chronic Spinal Cord Injury

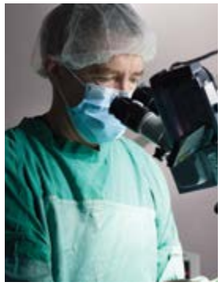
My research focuses on translational investigations and bridging the gap between basic science, clinical science, and the public community living with SCI. My current projects focus on 1) SCI consumer engagement in research, 2) determining the minimum amount of exercise and locomotor training required for clinical trials targeting chronic SCI, and 3) identifying the facilitators and barriers to clinical trial participation from the SCI consumer perspective. In addition, I direct our entire Schwann cell clinical trial program (5 trials) in collaboration with Dr. Levi.

NANCY L. BRACKETT, PH.D., H.C.L.D.

Research Professor, Departments of Neurological Surgery and Urology

Male Fertility following Spinal Cord Injury

Our research is focused on understanding and improving impairments to male fertility which occur following SCI. A major aim is to determine the cause of impaired semen quality in men with SCI. Our recent evidence indicates that the problem is related to the seminal plasma. 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.



JAMES D. GUEST, M.D., PH.D., F.A.C.S.

Clinical Professor, Department of Neurological Surgery

The Preclinical to Clinical Spectrum in Spinal Cord Injury Therapeutics: The Path to Clinical Testing and Establishing Clinical Evidence.

Our SCI research spans preclinical proof-of-concept (POC) studies of therapeutics into early Phase, and pivotal clinical trials of SCI. We are translational scientists using a variety of clinically-relevant tools within the complex process of determining which potential human therapeutics have a probability of success in clinical trial testing. We use our experience and expertise to test combinations of cellular, molecular, tissue engineering and neuromodulatory therapeutics in large animal models. We have expertise in tissue physiologic monitoring, neurophysiology and kinematic analysis of gait. In addition, we have experience in device development and testing. The lab group has members and colleagues ranging from senior medical faculty to postdoctoral students, medical students, neurosurgery residents, and undergraduate students. This is a good setting for those trainees who aim for careers in neurologic therapeutics both in academia and industry and with an interest in how medical evidence is developed. We are simultaneously involved with animal and human studies across the translational spectrum including Phase 1-3 studies.

GILLIAN A. HOTZ, PH.D.

Research Professor, Department of Neurological Surgery

Director, KiDZ Neuroscience Center; Director, Concussion, WalkSafe™ & BikeSafe™Programs

Neurocognitive Deficits Associated with Brain Injury; Injury Prevention

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. I have co-authored two neurocognitive tests, The Brief Test of Head Injury for adults and the Pediatric Test of Brain Injury for children. My research has focused on developing evidenced based injury prevention programs in order to prevent brain and spinal cord injuries in children. In 2003, our team developed the WalkSafe program, which has been shown to decrease the number of elementary school age children that get hit by cars, and in 2009 we developed the BikeSafe program which educated middle school age children on bicycle safety skills. As the Director of the Concussion Program we have spent many year developing and implementing a comprehensive countywide high school sports concussion care program, which includes neurologic evaluation, neuroimaging, neuropharmacological management, neuropsychological testing, and baseline test with ImPACT, a computerized neurocognitive screening measure. We also have developed a Concussion Injury Surveillance system. Our program is multidisciplinary and assesses and treats athletes from all levels of play. I am also the PI on many local and federal grants: Safe Routes to School initiatives, Transportation Alternative Programs, GE/NFL MRI Phase 2 study, Brainscope EEG study, one of the TRACK TBI sites, and a new project that will study the effects of cannabinoids on mild TBI.

ALBERTO MARTINEZ-ARIZALA, M.D.

Clinical Professor, Departments of Neurology, Neurological Surgery, and Physical Medicine & Rehabilitation

Chief, SCI Service Miami VA Medical Center

Pathophysiology and Treatment of Secondary Complications in Spinal Cord Injury

My research interests focus on common complications that are seen following spinal cord injury: pain, spasticity, syringomyelia, and tethered cord syndrome. 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.

EVA WIDERSTRÖM-NOGA, D.D.S., PH.D.

Research Professor, Departments of Neurological Surgery, Physical Medicine & Rehabilitation, and Health Scientist Veterans Affairs

SCI-related Neuropathic Pain Phenotypes and Biomarkers

My research program is focused on the identification of clinical correlates of underlying mechanisms of neuropathic pain associated with neurological trauma in order to facilitate the translation of basic research findings to treatments tailored to specific mechanisms. We are also examining the personal experiences of people living with chronic pain and SCI to increase our understanding about factors that help or hinder obtaining optimal pain relief. My research program is highly collaborative and includes extensive interdisciplinary protocols for a multimodal evaluation of self-reported pain symptoms and its psychosocial impact, quantitative assessment of neurological function, and biomarkers including non-invasive brain imaging.

COLEEN ATKINS, PH.D.

Associate Professor, Department of Neurological Surgery

Developing Novel Therapies for Traumatic Brain Injury and Spinal Cord Injury

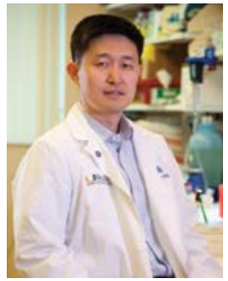
The research in my laboratory focuses on developing novel therapeutic interventions for traumatic brain injury (TBI) and spinal cord injury (SCI). The research goal of my laboratory is to enhance rehabilitation and recovery by manipulating synaptic plasticity at specific levels of the neuroaxis following TBI and SCI. We have found that specific synaptic plasticity signaling pathways are altered after TBI and we are currently using pharmacotherapies to target those pathways to improve behavioral recovery after TBI.

NAGI AYAD, PH.D.

Associate Professor, Department of Psychiatry and Behavioral Sciences

Epigenetic and Kinase Pathways in the Developing and Diseased Nervous Systems

The main research objective of the Ayad laboratory is to identify therapeutic combinations for nervous system disorders. These include brain cancers such as glioblastoma and medulloblastoma, as well as spinal cord injury and traumatic brain injury. We are working closely with chemists to generate novel brain/spinal cord penetrant epigenetic enzyme and kinase inhibitors. We are also working with the LINCS consortium to identify small molecules that target epigenetic and kinase pathways simultaneously. We collaborate with a large group of basic scientists and clinicians to move our small molecules into clinical trials. These include Dr. Ricardo Komotar, Dr. Michael Ivan, Dr. Antonio Omuro, Dr. Macarena de la Fuente, Dr. Nori Kasahara, Dr. Claes Wahlestedt, Dr. Stephan Schürer, Dr. Mary E. Hatten, Dr. Martine Roussel, and Dr. Jann Sarkaria for the brain tumor work, and Drs. Jae Lee, Vance Lemmon, and John Bixby for the spinal cord injury studies. Interestingly, we find that the same small epigenetic/kinase molecule inhibitors we are developing for brain cancer are effective in spinal cord injury as they reduce inflammation.



JAE K. LEE, PH.D.

Associate Professor, Department of Neurological Surgery

Promoting Proper CNS Wound Healing Response to Enhance Regeneration

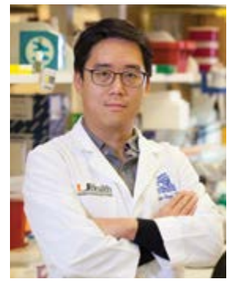
The long term research goal in my laboratory is to elucidate the mechanisms of cellular interactions in the injured CNS that create an environment inhibitory to cellular regeneration. Similar to other tissue, injury to the CNS triggers a wound healing response characterized by inflammation, cellular proliferation, and matrix remodeling. Sometimes this wound healing response is incomplete and leads to tissue cavitation, while other times it is excessive and leads to scar formation (both gliotic and fibrotic). A better understanding of this scarring process will help identify novel therapeutic targets that can promote a more permissive environment for CNS regeneration.

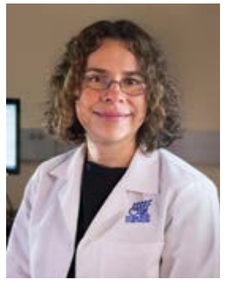
KEVIN K. PARK, PH.D.

Associate Professor, Department of Neurological Surgery

Intrinsic Mechanisms of Axon Regeneration

My lab is interested in understanding mechanisms that account for axon growth, guidance and circuit formation in the central nervous system (CNS). Previously, I and others have identified several key proteins that regulate axon regeneration, which are present in mature CNS neurons. In my current research, I seek to better understand the cellular and molecular mechanisms governing axon growth and connectivity during development and in adults after injury, and to explore the potential of developing therapeutic strategies for spinal cord injury and other neurodegenerative conditions.





MONICA A. PEREZ, P.T., Ph.D.

Professor, Departments of Neurological Surgery, Biomedical Engineering, Physical Therapy, Health Scientist Veterans Affairs

Motor Control in Humans with and without Spinal Cord Injury

The focus of our research is on understanding how the brain and spinal cord contribute to the control of voluntary movements in humans with and without spinal cord injury. This theme is mainly investigated from a neurophysiological point of view, using a combination of transcranial magnetic stimulation (TMS), magnetic resonance imaging (MRI), and peripheral nerve stimulation techniques. The population of individuals with SCI is heterogeneous. The severity of impairments depends on the site and extent of the injury. We use electrophysiological outcomes to design neuroplasticity protocols aiming to enhance functional outcomes. Current research projects focus on topics such as studying (1) the contribution of the primary motor cortex, the corticospinal system, and subcortical pathways to the control grasping, (2) the organization of paired-pulse TMS-induced indirect (I) waves, and (3) the use of spike-timing dependent plasticity to enhance the activity of residual corticospinal projections after spinal cord injury.

PANTELIS TSOULFAS, M.D.

Associate Professor, Departments of Neurological Surgery and Cell Biology & Anatomy

Neurotrophins: Specificity of Action

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.

JONATHAN R. JAGID, M.D.

Clinical Associate Professor, Department of Neurological Surgery, Neurology, Orthopedics, Rehabilitation Medicine

Interventions in SCI and TBI

My research includes projects investigating the use of Deep Brain Stimulation for spinal cord injury, novel brain machine interfaces to improve quality life in spinal cord injury, as well as hypothermia for traumatic brain injury. Presently, we are looking at the use of a novel Deep Bain Stimulation device modified to act as a brain machine interface in an effort to bypass spinal cord injury and restore cortically controlled limb movement. In traumatic brain injury, a prospective multicenter study is underway looking at the effects of modest hypothermia on the surgical evacuation of subdural hematomas (HOPES Trial).

BRIAN R. NOGA, PH.D.

Research Associate Professor, Department of Neurological Surgery

Brain and Spinal Mechanisms Controlling Walking

Neuromodulation technologies are increasingly looked at as potential treatment options for paralysis associated with spinal cord injury (SCI). Deep brain stimulation is one such method that so far has had little or no application in persons with SCI even though most new and chronic injuries are incomplete. Recent work in our laboratory has pointed to a brain target for controlling walking. We are currently investigating the usefulness of stimulating this site to enhance walking in a translational large animal model of SCI.

MARTIN OUDEGA, PH.D.

Research Associate Professor, Department of Neurological Surgery

Bioengineering Cell-based Spinal Cord Repair

We employ animal models to better our understanding of the neuroanatomical and functional consequences of spinal cord injury and to use this information to generate and guide cell-based strategies to maximize functional recovery. Bioengineering principles are tightly integrated in our studies; the versatility of natural and artificial biomaterials offers important possibilities to address questions related to the failed or limited repair by cell transplants. The overall goal of our scientific efforts is to develop repair approaches that lead to significant anatomical restoration resulting in functional restoration after spinal cord injury that can be translated into the clinic.

ROBERTA BRAMBILLA, PH.D.

Associate Professor, Department of Neurological Surgery

Modulation of the Neuro-Immune Response in Neurologic Disease

The main focus of my research is to understand the role of neuroinflammation in the pathophysiology of neurodegenerative disorders (e.g., multiple sclerosis, spinal cord injury and stroke), with a specific interest in the contribution of glial cells. We study astrocytes and microglia for their involvement in the neuro-inflammatory response to injury, and oligodendrocytes and oligodendrocyte precursor cells for their role in axon myelination, metabolic support of neurons and myelin repair. Currently, our primary lines of research in the area of neuroimmunology are centered on: (1) investigating the role of tumor necrosis factor and its receptors in the processes of neuroinflammation, demyelination and remyelination, and (2) understanding how mitochondrial dysfunction in oligodendrocytes may be involved in the etiopathology of multiple sclerosis.

HASSAN AL-ALI, PH.D.

Research Assistant Professor, Department of Neurological Surgery

Drug Discovery for CNS Repair

As a chemical and computational biologist, my lab focuses on identifying pharmacological targets that can induce robust axon regeneration in the injured central nervous system. To accomplish this, I developed a unique drug discovery platform that combines phenotypic screening, target-based profiling, and sophisticated machine learning algorithms. The approach identified a promising drug candidate that is now in preclinical development. We continue to develop these methodologies to advance drug discovery in spinal cord injury, as well as in other therapeutic areas including cancer and kidney disease.

RACHEL E. COWAN, PH.D.

Research Assistant Professor, Department of Neurological Surgery (until July, 2018)

Enhancement and Preservation of Maximal Transfer and Wheelchair Propulsion Ability

Our first focus is defining what level of fitness and 'skill' are required to independently perform transfers to and from the bed, car, shower, and ground and if these are different for various levels of SCI. Our second focus is defining how changes in fitness and wheelchair configuration can meaningfully reduce the effort required to propel a manual wheelchair and how these changes may differ by level of SCI.

JUAN PABLO DE RIVERO VACCARI, PH.D.

Research Assistant Professor, Department of Neurological Surgery

Underlying Mechanisms of the Innate Immune Response and Contributions to Various CNS Diseases

My research focuses on understanding early inflammatory events in central nervous system (CNS) injury and disease, as well as aging. Currently, my laboratory studies how natural-aging produces inflammation in the brain, a phenomenon known as brain inflammaging, which potentially precedes the onset of age-related neurodegenerative diseases. In addition, we are studying the mechanism by which brain injury causes systemic inflammation such as acute lung injury. Moreover, we also study the prognostic and diagnostic potential of inflammasome proteins as biomarkers of CNS injury and disease, including brain and spinal cord injury, stroke, multiple sclerosis, mild cognitive impairment and depression.

MOUSUMI GHOSH, PH.D.

Research Assistant Professor, Department of Neurological Surgery

Altering Host Glial Responses following CNS Injury and Disease to Promote Repair

My research interests are focused on altering the hostile environment of the injured or diseased CNS to one that is conducive to repair through altering inflammation. Specifically our work focuses on delineating the intrinsic and extrinsic signals present after injury that antagonize the conversion of activated microglia and macrophages to a reparative phenotype in experimental models of CNS injury and disease. We are also interested in understanding how altering the immunophenotypical profile of macrophages and microglia can modulate spinal cord injury induced central neuropathic pain, affect host glial responses, including glial scar formation, as well as influence the ability of transplanted cells, such as Schwann cells and stem cells, to mediate neurorepair.

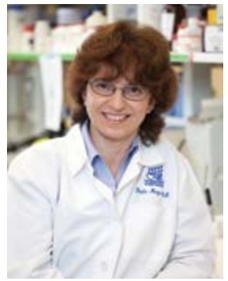
HOWARD B. LEVENE, M.D., PH.D., F.A.A.N.S.
Clinical Assistant Professor, Department of Neurological Surgery

Phosphodiesterase Inhibitors and Schwann Cell Transplantation after SCI

Secondary injury after spinal cord injury remains an active area for proposed therapy. With my co-PI Dr. Damien Pearse, we are investigating the effect of novel phosphodiesterase inhibitors after SCI. Phosphodiesterase inhibitors are proposed to sustain cAMP to abate cytotoxic processes during secondary injury, resulting in neuroprotection. Our work involves both murine and porcine models. Another proposed therapy for spinal cord injury is to introduce cells to the injury site to help repair, restore, or support existing neurons. I worked with my colleagues on a large animal model to study the effect and behavior of transplanted autologous Schwann cells. I have been involved in the refinement of this animal model. This approach allows for the scientific study of the behavior of implanted cells and generates the groundwork for clinical trials. Research utilizing this model is done in collaboration with clinicians and scientists at the Miami Project such as Drs. Guest, Solano, Pearse, Levi, Wood, Bunge, and many more. I am also collaborating with the University of Miami, School of Engineering, Drs. Charles Huang and Weiyong Gu, studying the nutritional factors in spinal disc degeneration.

PAULA V. MONJE, PH.D.
Research Assistant Professor, Department of Neurological Surgery (until Dec, 2018)

Schwann Cell Biology and Their Applications in Cell Therapy



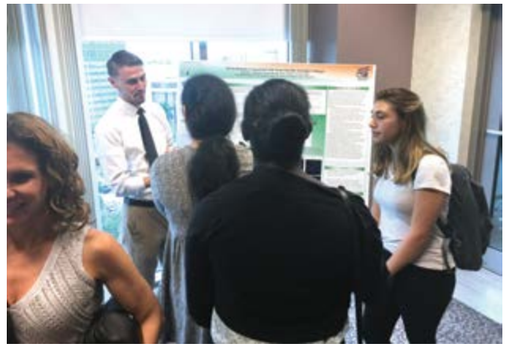
Work in my laboratory combines signal transduction research on mechanisms of Schwann cell differentiation and assay development strategies for the use of Schwann cells in cell therapy. We study the role of the second messenger cAMP in the reciprocal interactions between Schwann cells and neurons underlying the regulation of Schwann cell proliferation, myelination and repair. We also work on the development of new cellular platforms, assays and methods to isolate, purify and characterize the phenotype and function of Schwann cells from human donors and experimental animals. One important goal is to improve the potency and myelinating capability of the cells in culture prior to transplantation in the central and peripheral nervous systems.

Summer Student Research

A major role of The Miami Project is to provide education and training for the next generation of neuroscientists. Our long-term educational goal is to increase the number of scientists and laboratories working on paralysis research and central nervous system disorders around the world. Students and young scientists beginning their careers gain skills from The Miami Project's state-of-the-art comprehensive research and academic environment.

Summer Students and their Research Projects:

Name	Summer mentor	Summer project
Mark Bertematti	Dr. Mark S. Nash	"Neuromodulation for Cardiovascular Dysfunction after Experimental Spinal Cord Injury: A Feasibility Study"
Mahitha Kunamneni	Dr. Daniel Liebl	The Role of TMEM97 in Cell Death After Traumatic Brain Injury"
Sidney London	Dr. Coleen Atkins	"Selective Allosteric Modulation of the A7 Nicotinic Acetylcholine Receptor Reverses TBI-Induced Pathology"
Alexander Margetts	Dr. Damian Pearse	"Seminiferous Tubule Degradation Post-SCI"
Jeffery Serville	Dr. Monica Perez	"Body-Machine Interface Training in Humans with Spinal Cord Injury"



Alexander Margetts presents his research poster at the 8th Annual Miami Project Summer Student Research Session

Sidney London describes her summer research project to Miami Project faculty, staff, and students

In 2018, Drs. Katie Gant, Director of Education, and Dr. W. Dalton Dietrich, Scientific Director, organized another very successful NIH Summer Student Research Program. The summer research experience was designed to provide a diverse group of exceptional undergraduate students with the opportunity to work alongside Miami Project's leading scientific researchers. This year, the program was open to students with a history of volunteering at The Miami Project under a no-cost extension. During this 10-week program, students attended a number of lectures and journal clubs, in addition to conducting full-time, "hands-on" laboratory research on various NIH-funded projects. At the end of the program, each student created an abstract explaining their specific research project and presented their work in an oral presentation, as well as a poster, as part of the 8th Annual Miami Project Summer Student Research Session on July 29, 2018.

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.

Visiting lecturer Dr. Greg Lemke with MP scientists

October 4, 2017
Ben Emery, PhD
Oregon Health and Science University – Portland, OR

November 1, 2017
Greg Lemke, PhD
The Salk Institute for Biological Sciences – San Diego, CA

December 6, 2017
Ed Boyden, PhD
Massachusetts Institute of Technology – Cambridge, MA

January 17, 2018|
Ona Bloom, PhD
The Feinstein Institute for Medical Research – Manhasset, NY

February 7, 2018
Dana McTigue, PhD
Ohio State University – Columbus, OH

March 14, 2018
Ki-Bum Lee, PhD
Rutgers, The State University of New Jersey – Piscataway, NJ

May 2, 2018
Grégoire Courtine, PhD
Swiss Federal Institute of Technology Lausanne – Geneva, Switzerland

Scientific Publications

Published studies that have passed the test of peer review are the benchmark of scientific progress. Listed here are the 2018 research publications by Miami Project scientists and colleagues.

Aguiar SA, Baker SN, Gant KL, Bohorquez J, Thomas CK. (2018). Spasms after spinal cord injury show low-frequency intermuscular coherence. *Journal of Neurophysiology*. 120(4):1765-1771.

Aguiar SA, Choudhury S, Kumar H, Perez MA, Baker SN. (2018). Effect of central lesions on a spinal circuit facilitating human wrist flexors. *Scientific Reports*. 8(1):14821.

Al-Ali H, Debevec G, Santos RG, Houghten RA, Davis JC, Nefzi A, Lemmon VP, Bixby JL, Giulianotti MA. (2018). Scaffold ranking and positional scanning identify novel neurite outgrowth promoters with nanomolar potency. *ACS Medical Chemistry Letters.* 9(10):1057-1062.

Allen CJ, Baldor DJ, Hanna MM, Namias N, Bullock MR, Jagid JR, Proctor KG. (2018). Early craniectomy improves intracranial and cerebral perfusion pressure after severe traumatic brain injury. *The American Surgeon.* 84(3):443-450.
Almeida VW, Bates ML, Bunge MB. (2018). Preservation, sectioning, and staining of Schwann cell cultures for transmission electron microscopy analysis. *Methods in Molecular Biology (Clifton, N.J.)*. 1739:195-212.

Andersen ND, Monje PV. (2018). Isolation, culture, and cryopreservation of adult rodent Schwann cells derived from immediately dissociated teased fibers. *Methods in Molecular Biology (Clifton, N.J.).* 1739:49-66.

Assis-Nascimento P, Tsenkina Y, Liebl DJ. (2018). EphB3 signaling induces cortical endothelial cell death and disrupts the blood-brain barrier after traumatic brain injury. *Cell Death & Disease*. 9(1):7.

Bademci G, Abad C, Incesulu A, Rad A, Alper O, Kolb SM, Cengiz FB, Diaz-Horta O, Silan F, Mihci E, Ocak E, Najafi M, Maroofian R, Yilmaz E, Nur BG, Duman D, Guo S, Sant DW, Wang G, Monje PV, Haaf T, Blanton SH, Vona B, Walz K, Tekin M. (2018). MPZL2 is a novel gene associated with autosomal recessive nonsyndromic moderate hearing loss. *Human Genetics.* 137(6-7):479-486.

Basil G, Madhavan K, Komotar R, Levi AD (2018). The utility of magnetic resonance imaging compatible pacemakers in neurosurgical patients. *Cureus.* 10(9):e3374.

Bastidas J, Athauda G, Gabriela De la Cruz, Chan W-M, Golshani R, Berrocal Y, Henao M, Lalwani A, Manoji C, Assi, Khan A, Anderson K, Marcillo AE, Norenberg M, Levi AD, Wood PM, Guest JD, Dietrich WD, Bunge MB, Pearse DD. (2018). Translation of human Schwann cells to clinical trials for human spinal cord injury: preclinical evaluation of safety and neuro-reparative action. *Glia.* 65(8) 1278-1301.

Bauman WA and Nash MS. (2018). Endocrinology and metabolism of persons with spinal cord injury. *In*: Kirshbaum S and Lin V (Eds.), *Spinal Cord Medicine (3rd Edition).* Lippincott, Williams, and Wilkins, Publishers, Philadelphia, PA., pp. 279-317.

Bennett C, Samikkannu M, Mohammed F, Dietrich WD, Rajguru SM, Prasad A. (2018). Blood brain barrier (BBB)-disruption in intracortical silicon microelectrode implants. *Biomaterials*. 164:1-10.

Bennett C, Mohammed F, Álvarez-Ciara A, Nguyen MA, Dietrich WD, Rajguru SM, Streit WJ, Prasad A. (In press). Neuroinflammation, oxidative stress, and blood-brain barrier (BBB) disruption in acute Utah electrode array implants and the effect of deferoxamine as an iron chelator on acute foreign body response. *Biomaterials.*

Berry K, Luther EM, Urakov T, Bullock MR. (2018). Rare event captured with intracranial pressure monitor: malignant spike in intracranial pressure during delayed chest closure in heart-transplant patient with ischemic stroke. *World Neurosurgery.* 114:301-304.

Bigford GE, Darr AJ, Bracchi-Ricard VC, Gao H, Nash MS, Bethea JR. (2018). Effects of ursolic acid on sub-lesional muscle pathology in a contusion model of spinal cord injury. *PLoS One.* 13(8):e0203042.

Blaya MO, Wasserman MW, Pieper AA, Sick TJ, Bramlett HW, Dietrich WD. (In press). Neurotherapeutic capacity of P7C3 agents for the treatment of traumatic brain injury. *Neuropharmacology.*

Brooks AE, Athauda G, Bunge MB, Khan A. (2018). Culture and expansion of rodent and porcine Schwann cells for preclinical animal studies. *Methods in Molecular Biology (Clifton, N.J.)*. 1739:111-126.

Brackett NL, Ibrahim E, Lynne CM. (2018). Sperm retrieval from the bladder. *In:* Skinner MK (Ed.), *Encyclopedia of Reproduction (2nd Edition).* Elsevier, Vol. 4, pp. 403-407.

Brusko GD, Burks SS, Wang MY. (2018). Engineered neurons may generate future therapy for neurological disease. *Neurosurgery*. 83(3):E105-E106.

Brusko GD, Kolcun JPG, Wang MY. (2018). Machine-learning models: the future of predictive analytics in neurosurgery. *Neurosurgery.* 83(1):E3-E4.

Brusko GD, Kolcun JPG, Wang MY. (2018). Novel photoconductive material demonstrates potential for dose reduction in x-ray imaging. *Neurosurgery.* 82(3):N22-N23.

Brusko GD, Yoon JW, Wang MY. (In press). Through the eyes of a neurosurgeon - how binocular disparity translates into surgical performance. *Neurosurgery.*

Bunday KL, Urbin MA, Perez MA. (2018). Potentiating paired corticospinal-motoneuronal plasticity after spinal cord injury. *Brain Stimulation.* 11(5):1083-1092.

Burks JD, Gant KL, Guest JD, Jamshidi AG, Cox EM, Anderson KD, Dietrich WD, Bunge MB, Green BA, Khan A, Pearse DD, Saraf-Lavi E, Levi AD. (In press). Imaging characteristics of chronic spinal cord injury identified during screening for a cell transplantation clinical trial. *Journal of Neurosurgery, Neurosurgical Focus.*

Callahan MK, Cowan RE. (2018). Relationship of fitness and wheelchair mobility with encounters, avoidances, and perception of environmental barriers among manual wheelchair users with spinal cord injury. *Archives of Physical Medicine Rehabilitation.* 99(10):2007-2014.

Cerqueira SR, Lee YS, Bunge MB. (2018). A culture model to study neuron-Schwann cell-astrocyte interactions. *Methods in Molecular Biology (Clifton, N.J.)*. 1739:269-279.

Cerqueira SR, Lee YS, Cornelison RC, Mertz MW, Wachs RA, Schmidt CE, Bunge MB. (2018). Decellularized peripheral nerve supports Schwann cell transplants and axon growth following spinal cord injury. *Biomaterials.* 177:176-185.

Chan AK, Bisson EF, Bydon M, Glassman SD, Foley KT, Potts EA, Shaffrey CI, Shaffrey ME, Coric D, Knightly JJ, Park P, Wang MY, Fu KM, Slotkin JR, Asher AL, Virk MS, Kerezoudis P, DiGiorgio AM, Haid RW, Mummaneni PV. (In press). Obese patients benefit, but do not fare as well as nonobese patients, following lumbar spondylolisthesis surgery: an analysis of the quality outcomes database. *Neurosurgery.*

Chan AK, Bisson EF, Bydon M, Glassman SD, Foley KT, Potts EA, Shaffrey CI, Shaffrey ME, Coric D, Knightly JJ, Park P, Wang MY, Fu KM, Slotkin JR, Asher AL, Virk MS, Kerezoudis P, Chotai S, DiGiorgio AM, Haid RW, Mummaneni PV. (2018). Laminectomy alone versus fusion for grade 1 lumbar spondylolisthesis in 426 patients from the prospective quality outcomes database. *Journal of Neurosurgery Spine.* 30(2):234-241.

Chang HK, Kolcun JPG, Chang PY, Wang MY. (2018). Enhanced recovery after Surgery™ awake minimally-invasive transforaminal lumbar interbody fusion: 2-dimensional operative video. *Operative Neurosurgery.*

Chin C, Lunking ES, de la Fuente M, Ayad NG. (2018). Immunotherapy and epigenetic pathway modulation in glioblastoma multiforme. *Frontiers in Oncology*. 8:521.

Chiou SY, Strutton PH, Perez MA. (2018). Crossed corticospinal facilitation between arm and trunk muscles in humans. *Journal of Neurophysiology.* 120(5):2595-2602.

Christiansen L, Perez MA. (2018). Targeted-plasticity in the corticospinal tract after human spinal cord injury. *Neurotherapeutics*. 15(3):618-627.

Christiansen L, Urbin MA, Mitchell GS, Perez MA. (2018). Acute intermittent hypoxia enhances corticospinal synaptic plasticity in humans. *eLife.* 7:e34304.

Cowan RE, Anderson KD. (In press). Replication and novel analysis of age and sex effects on the neurologic and functional value of each spinal segment in the US healthcare setting. *Spinal Cord*.

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Dietrich WD. (2018). Clinical significance and potential translation of neural regeneration and functional recovery in monkeys after spinal cord injury. *Science China. Life Sciences*. 61(10):1291-1292.

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Donnally CJ, Madhavan K, Butler AJ, Sheu JI, Massel DH, Green BA, Gjolaj JP. (In press). A novel technique for stabilization of high-grade spondylolisthesis with transvertebral fusion without reduction. *Journal of Clinical Neuroscience.*

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overground system for detecting spinal cord injury-associated thermal and mechanical hypersensitivity in rats. *European Journal of Pain.* 22(9):1628-1640.

Eichberg DG, Starke RM, Levi AD. (2018). Combined surgical and endovascular approach for treatment of aggressive vertebral haemangiomas. *British Journal of Neurosurgery.* 32(4):381-388.

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Kolcun JPG, Brusko GD, Wang MY. (In press). Non-opioids prove non-inferior for chronic pain: results of the SPACE trial. *World Neurosurgery.*

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For those who can't

The Miami Project to Cure Paralysis was established in 1985 to develop new therapies to improve function in paralyzed individuals. We are very enthusiastic about our current accomplishments and multi-disciplinary research programs. In addition, we are most eager about the future as we continue to move new treatments forward to treat paralysis.

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