

Defense Health Program

Spinal Cord Injury Research Program

Advancing the treatment and management of SCI and ameliorating its consequences relevant to injured Service members.



Congressionally Directed Medical Research Programs

History of the CDMRP

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. The success in managing the initial congressional appropriations in breast cancer research combined with additional advocacy movements and the need for focused biomedical research catapulted the CDMRP into a global funding organization for cancer, military medical, and other disease-specific research. The CDMRP has grown to encompass multiple targeted programs and has received over \$8 billion in appropriations from its inception through fiscal year 2014 (FY14). Funds for the CDMRP are added to the Department of Defense (DoD) budget in which support for individual programs, such as the Spinal Cord Injury Research Program (SCIRP), is allocated via specific guidance from Congress.

Application Review Process

The CDMRP uses a two-tier review process for application evaluation with both steps involving dynamic interaction between scientists and clinicians—subject matter experts—and consumers. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel, which compares applications to each other and makes funding recommendations based on scientific merit, portfolio balance, and relevance to program goals.



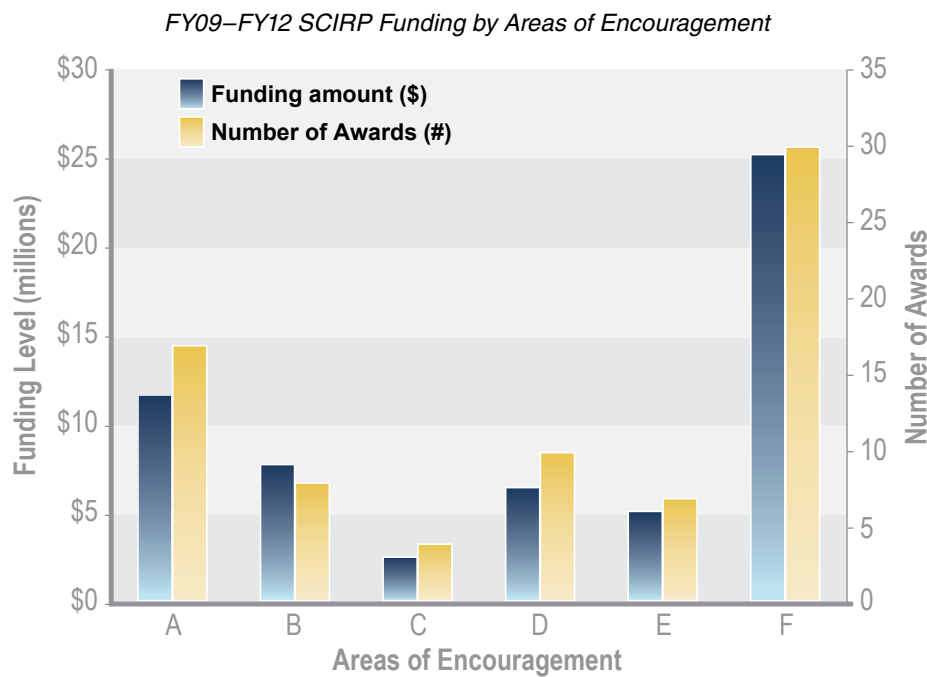
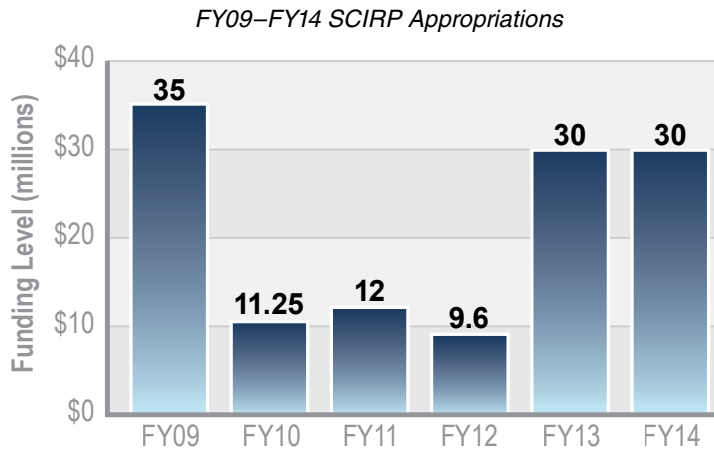
Consumer Advocacy Participation

A unique aspect of the CDMRP is the active participation of consumer advocates or patient/survivor representatives throughout the program's annual cycle. Consumers work collaboratively with leading scientists and clinicians in setting the SCIRP's vision and mission, reviewing applications, and making final funding recommendations. From the unique perspective gained through personal experience, the consumer brings a sense of urgency and focus to all levels of decision-making. Consumers evaluate applications based on the potential impact and benefit to the patient population, encouraging funding recommendations that reflect the concerns and needs of the spinal cord injury population, their families and caregivers, and the clinicians who treat them.

Spinal Cord Injury Research Program

History of the DoD SCIRP

Spinal cord injuries are serious and complex neurotraumatic wounds affecting military Service members serving in Iraq and Afghanistan. The SCIRP was established by Congress in FY09 with a \$35 million (M) appropriation to support research into regenerating/repairing damaged spinal cords and improving rehabilitation therapies. From FY10–FY14, Congress appropriated an additional \$92.85M to continue this research (see graph at right). The SCIRP focuses its funding on projects that have the potential to make a significant impact on improving the function, wellness, and overall quality of life for military Service members as well as their caregivers, families, and the American public. SCIRP funding between FY09 and FY12 by areas of encouragement is shown in the figure below.



- A = Pre-hospital, en route care, and early hospital management of SCI
- B = Development, validation, and timing of promising interventions to address issues during the first year after SCI
- C = Identification and validation of best practices during the first year after SCI
- D = Bladder, bowel, and sexual dysfunction
- E = Neuropathic pain and sensory dysfunction
- F = Functional deficits

VISION

Advance the treatment and management of spinal cord injury and ameliorate its consequences relevant to injured Service members.

MISSION

To fund research and foster collaborative environments for the development and translation of more effective strategies to improve the health and well-being of Service members, Veterans, and other individuals with spinal cord injury.



Consumer Highlights

Joan Grey, Tampa General Hospital



Withstanding SCI to Continue a Life of Service and Helping Others

Joan Grey has taken on many roles in her life—mother, grandmother, Veteran, and military spouse. She graduated from West Point in the first class that included women and was commissioned in the Army where she served in the U.S. and Germany as platoon leader, commander, and staff officer. At five years of service, she sustained an SCI in a midair collision during a parachute jump, and was medically retired from military service. The accident, which occurred during a night mass tactical operation at Fort Bragg, North Carolina, not only ended her military career but also curtailed some of her favorite pastimes, such as running. Over a period of 8 months, her injuries resolved somewhat. The 12 vertebrae fusion with hardware, cauda equina syndrome, and ankle repairs are an ongoing reminder of her airborne legacy. Today, she is an ambulatory paraplegic, meaning that she is mobile but is living with some hidden disability as a result of her injury. She is a lifetime member of Paralyzed Veterans of America (PVA).

Joan has maintained an active lifestyle, through which she exercises her passion for helping others. She serves as Director of Creative Initiatives with Spiral Alliance Partners, where she engages in projects that include workshop development (e.g., Women’s Leadership Practicum, Women’s Healing) and social media (e.g., Joining Forces Mentoring Plus™). As a military spouse, she has served as hospital chaplain and environmental educator, fund raiser, and facilitator. She has also volunteered with family readiness groups, military spouse organizations, and the American Red Cross. She initiated and coordinated programs including SEA (support, encouragement, accountability) circles, art & soul, Caring Connections, and Soulcrafts. She currently facilitates a spirituality group and a virtual SEA accountability circle, volunteers at Arlington Cemetery, and blogs for Index Card Cure™.

Joan and her husband have settled in Arlington, Virginia. It was here that she learned about CDMRP and its mission from a neighbor, who is serving as a reviewer for one of its programs. Through this connection, Joan was introduced to, and recommended as a consumer reviewer for, the DoD SCIRP. She served as a peer reviewer for the FY11 and FY12 programs. “I hope that my participation makes a difference in furthering research and awareness about SCIs,” Joan said.

Joan’s son, a Coast Guard aviator, and his family live in Florida. Envisioning the world she wants her “grand girls” to experience and inherit is Joan’s driving force, and the focus of her attention and energy. Marshaling the discipline and perseverance honed as a runner, Joan continues her work to improve the lives of military families, women Veterans, and individuals with SCI.

“It was an honor to participate as a consumer advocate in the DoD SCIRP program and provide insights to the clinical investigators.”



Sherman Gillums, Paralyzed Veterans of America **Learning the Importance of Life** **through SCI**

The driving force for consumer advocate Sherman Gillums, Jr., is to “take what he has learned and give back.” Sherman enlisted in the Marines at age 17; twelve years later, shortly after the 9/11 terrorist attacks and while preparing to deploy to Afghanistan with the 1st Marine Division, he suffered a spinal cord injury in an automobile accident. At age 29, this recipient of two Navy/Marine Corps Commendation Medals, a Navy/Marine Corps Achievement Medal and a Global War on Terror Service Medal, was paralyzed and honorably discharged from the Marine Corps. He turned to PVA, the advocacy organization founded by returning WWII Service members with spinal cord injuries, for support in re-entering the job market after his SCI. Not only did he find a career he enjoys—and returned to school for a Master’s degree—but, today Sherman is PVA’s Associate Executive Director for Veterans Benefits, overseeing field services, vocational rehabilitation services, and architecture services.

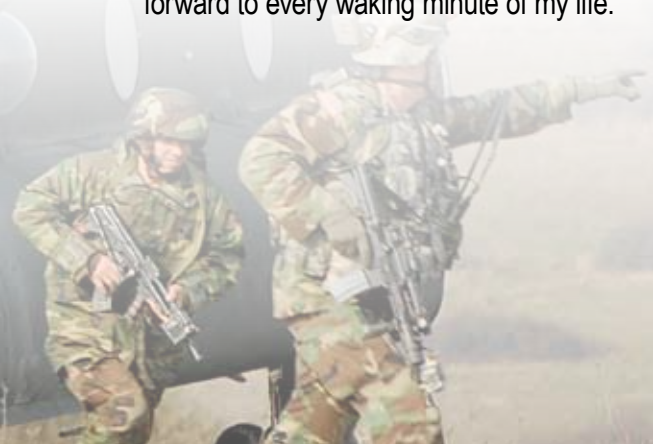
In his free time, Sherman loves spending time with his wife, two sons, and four daughters. He enjoys reading nonfiction, writing, and watching sports—especially football, basketball, and boxing. Acknowledging his family as the true catalyst behind his recovery, he reflects, “I relied on intestinal fortitude to get me through the challenges I faced in the Marines. But with SCI rehabilitation, it took that and more. My family’s belief in me gave me the ability to persevere beyond my normal limits.”

Sherman was nominated by PVA to serve as a peer reviewer for CDMRP’s SCIRP. Of his experience, he says that he thoroughly enjoyed the “privilege to represent the perspective of men and women with SCI while exploring various realms of scientific research.” Being a consumer peer reviewer also gave him the chance to speak with the dedicated researchers working to “improve quality of life for people with SCI, whether that entails totally eliminating neuropathic pain, restoring full hand function for someone with quadriplegia, or completely healing a spinal cord and its function after injury.”

He reflects upon the extraordinary courage and determination he mustered on his path to recovery, being able to reach out for help and not only survive, but become that person who can extend the helping hand. As Sherman ardently states, “My SCI has made me appreciate the importance of life...it also gives me the opportunity to inspire others—something I look forward to every waking minute of my life.”



“There is no better way to give back to those who saved my life, pushed me through rehabilitation, and helped me reintegrate into society than being a consumer advocate.”



Continuum of Care



Acute SCI Treatment

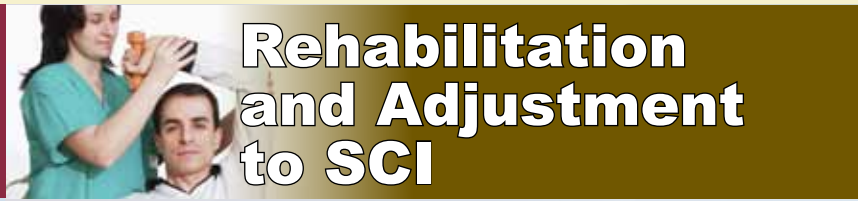
Victor Arvanian, Ph.D., D.Sc.: The sugar chains of chondroitin sulfate proteo-glycan (CSPG) have previously been shown to inhibit neural regeneration. Dr. Arvanian determined that a single administration of an antibody to the NG2 chain of CSPG restores the neural deficits induced by NG2.

Adina Michael-Titus, D.Sc.: Found that treatment of mice with docosahexaenoic acid (an omega-3 polyunsaturated fatty acid) within 30 minutes after contusion injury resulted in significant locomotor improvement as early as 11 days post-injury.* (See page 9 for details.)

Linda Noble, Ph.D.: Demonstrated that administration of an inhibitor of matrix metalloproteinase in an animal model 8 hours following SCI resulted in improved neurological outcome in the animals by 6 weeks.* (See page 8 for details.)

Michael Beattie, Ph.D., Geoffrey Manley, M.D., Ph.D., and Graham Creasey, M.D.: Used information from current clinical practice to aid in the development of relevant animal models of SCI and TBI. The researchers continue to gather information to determine the greatest needs for this population.*

Diane Snow, Ph.D.: Demonstrated that injured astrocytes produce a wide variety of inhibitory CSPGs. Dr. Snow prepared a recombinant enzyme that can naturally degrade CSPGs in a rodent SCI model, leading to neuronal regeneration.



Rehabilitation and Adjustment to SCI

Gregory Clark, Ph.D. and Lee Miller, Ph.D.: Creating a novel brain-machine interface in an animal model by implanting high-count electrode arrays into a peripheral nerve in the animal's forearm that will activate paralyzed muscles in the forearm, wrist, and hand.*

Leslie Morse, D.O.: Conducting a clinical trial to determine the ability of functional electrical stimulation-rowing combined with zoledronic acid (slows bone loss) to reverse bone deterioration due to SCI. Early results indicate increased bone formation and stiffness with rowing.

Thomas Schnitzer, M.D., Ph.D.: Conducting a clinical trial focused on evaluating the combined effect of vibration therapy with administration of parathyroid hormone, and measuring the effects on bone using magnetic resonance imaging and serum bone biomarkers.



Spinal Regeneration

Douglas Smith, M.D.: Developed a spinal cord repair technique using tissue-engineered nerve grafts consisting of living dorsal root ganglia and axons that can be stretch-grown to a length necessary to bridge large lesions.*

Damien Pearse, Ph.D., Mary Bunge, Ph.D., and James Guest, M.D., Ph.D.: Conducted dosage, safety, and toxicity studies of Schwann cell implantation in animal models of SCI. After determining the optimal dose, they observed a significant improvement in locomotor function in animals treated with Schwann cells versus injured controls. A Phase I clinical trial is in progress to evaluate safety in individuals with sub-acute SCI.*



Chronic SCI and Secondary Complications

Radi Masri, DDS, M.S., Ph.D.:

Discovered a novel brain circuit that can be manipulated to manage pain following SCI. Found that stimulation of the motor cortex reduces pain by activating neurons in the zona incerta (an inhibitory nucleus in the brain).*

Charles Hubscher, Ph.D.: Evaluating rats with severe incomplete SCI to determine whether daily step training can lead to an improvement in bladder function and a reduction in external bladder maintenance.* (See page 10 for details.)

Stephen Sprigle, Ph.D.: Measuring weight-shift activities, including pressure reliefs such as leans or push-ups, to help better educate persons with SCI who use a wheelchair on how to prevent the development of pressure ulcers.

Gordon Mitchell, Ph.D., Gillian Muir, D.V.M., Ph.D., and Randy Trumbower, Ph.D.: Studying the ability of intermittent hypoxia, alone or combined with locomotor training, to improve limb function in animals with chronic SCI.* (See page 11 for details.)

Raymond Grill, Ph.D.: Exploring the molecular, biochemical, and structural changes in blood-testis-barrier (BTB) with time after SCI. Dr. Grill will also test the anti-inflammatory drug Licofelone for protection of BTB integrity.

Naoki Yoshimura, M.D., Ph.D.: Autonomic dysreflexia (AD) induces dangerously elevated blood pressure in those with SCI. Dr. Yoshimura determined that treatment of SCI rats with nerve growth factor antisense successfully reduces AD associated with bladder distension.

Quality of Life Research

Lisa Gould, M.D., Ph.D.: Identifying and stratifying risk factors for the development of pressure ulcers post-SCI. Developing a clinical assessment tool to assist healthcare providers in identifying individuals at greatest risk.*

Susan Charlifue, Ph.D.: Identifying issues specific to family caregivers of Veterans with SCI and developing a relevant, culturally appropriate instrument to assess caregiver distress and/or benefit.

Eva Widerstrom-Noga, D.D.S., Ph.D.: Identifying barriers and facilitators to coping and management of persistent pain and its impact on activities and participation after SCI.

Research Highlights:

Acute Care (Pre-Hospital, En Route, and

“SCIRP is a bridge that connects the SCI scientific field with the resources of a congressional appropriation of funds through the DoD. Investigators with various disciplines have been encouraged to participate by conducting innovative research for enhancing the quality of care and quality of life for individuals with SCI. These projects may vary from basic science, engineering designs, translational, clinical, battle field-related, or psychosocial-related problems. SCIRP also works as a catalyst. It helps identify areas of SCI research that either have tremendous clinical or scientific value, or the timing is ripe due to scientific breakthroughs and/or emerging technologies. By identifying these areas of encouragement, many outstanding researchers have now become SCI investigators who are interested in finding ways to better the lives of so many Americans with spinal cord injury and disorders.”

—**Vernon Lin, M.D.**
IP Member;
Cleveland Clinic



Matrix Metalloproteinases as a Therapeutic Target to Improve Neurologic and Urologic Recovery after Spinal Cord Injury

Linda Noble, Ph.D.,

University of California, San Francisco

Despite decades of effort being dedicated to developing therapeutics for SCI, a robust clinical treatment remains elusive. Following acute SCI, matrix metalloproteinases

(MMPs) are upregulated and promote early inflammation and disrupt the extracellular matrix and the blood-spinal cord barrier.

Dr. Linda Noble has received an FY10 Investigator-Initiated Research Award from the SCIRP to study the efficacy of an MMP inhibitor in a mouse model of SCI as well as a larger animal model with naturally occurring SCIs as the result of spontaneous rupture of an intervertebral disk. Newly completed studies in mice subjected to a relatively severe SCI show that the MMP inhibitor therapy, when provided 8 hours post injury, results in improved neurological outcome by 6 weeks. Moreover, bladder function, assayed by awake cystometry, also improves as evidenced in part by a reduction in uninhibited bladder contractions and residual urine.

Dr. Noble has entered into collaboration with Dr. Jon Levine at Texas A&M University to determine the efficacy of the MMP inhibitor in a second animal model of SCI. The researchers have established the safety and appropriate drug dosing parameters of the MMP inhibitor in uninjured animals. They have collected baseline urodynamic data in both uninjured animals and animals with acute SCI.

It is anticipated that the unique two-species design of this study will enable the rapid pre-clinical optimization of a promising MMP inhibitor for the treatment of SCI. If these pre-clinical studies in animal models are successful, this compound could be quickly transitioned into human clinical trials.



Early Hospital Management of SCI)

A New Neuroprotective Docosahexaenoic Acid Preparation Shows Promise for Improved Locomotor Function after Spinal Cord Injury

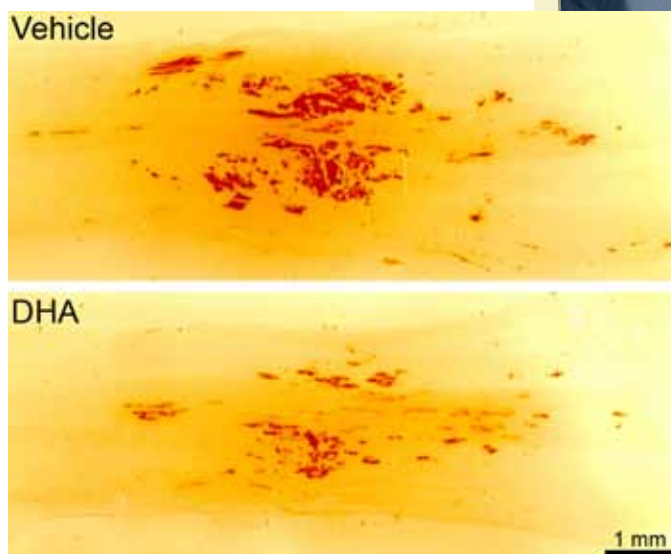
**Adina Michael-Titus, D.Sc.,
Queen Mary, University of London,
United Kingdom**



SCI is a devastating, life-altering condition with major financial and societal impacts. Dr. Adina Michael-Titus has previously shown that omega-3 polyunsaturated fatty acids (PUFAs) are potently neuroprotective when administered acutely following experimental SCI. PUFAs, such as docosahexaenoic acid (DHA), display antioxidant and anti-inflammatory effects and can reduce neuronal and glial cell death following injury.

Dr. Michael-Titus received an FY09 Investigator-Initiated Research Award from the SCIRP to determine the optimum formulation, dosage, and treatment regimen of DHA to improve functional outcomes following experimental SCI. In a mouse contusion model of SCI, her research team demonstrated that mice treated with DHA free fatty acid 30 minutes post-injury showed significant locomotor improvement beginning 11 days after injury, an effect that was still significant at 5 weeks following SCI. These results were confirmed using a rat contusion model of SCI in which improved locomotor function following DHA treatment was correlated with neuronal survival in the injured spinal cord. There was also evidence of vascular protection following the fatty acid treatment (see Figure, courtesy of Dr. Ping Yip). Further, improved locomotion was associated with an increase in microglia and macrophages in the rat model, suggesting an increase in inflammation in the DHA-treated injured spinal cord. This finding is particularly intriguing because it contradicts the hypothesis that improved functional outcome following SCI is associated with reduced inflammation.

DHA could provide an efficacious and safe treatment for SCI that could be administered early by an emergency response team, limiting the progression of injury and improving the capacity for functional recovery of individuals with SCI.



NovaRed staining was used to demonstrate a significant reduction in hemorrhage following SCI in rats treated with DHA (bottom) compared to those treated with control vehicle (top).

Research Highlights:

Chronic Care and Complications

"It's been a great honor to be on the Integration Panel for the DoD CDMRP, for spinal cord injury. The panel is made up of experts whose knowledge base crossed multiple disciplines, which led to insightful review of the proposals. The peer-reviewed research goal is to help find cures and preventative measures for spinal cord injury and its secondary complications. We commend the work that is done by the Integration Panel and the research that has made an impact on so many lives."

—**Maureen Simonson,**
R.N., M.S.N.
IP Member
Paralyzed Veterans
of America



Retaining Bladder Function after Spinal Cord Injury

Charles Hubscher, Ph.D.,
University of Louisville

Maintaining control of bladder function after an SCI is important to both the quality of life and health of the injured individuals. Research in this area to date has found an association between bladder function and a family of molecules called neurotrophic factors,

which are involved in the growth and maintenance of neurons. Dr. Charles Hubscher and his team noticed that individuals with severe incomplete injuries who underwent treadmill step training often had concurrent improvement in bladder function with a reduction in external bladder maintenance, in accordance with a documented account (Schalow G. 2010. *Electromyography and Clinical Neurophysiology* 50[3-4]:155-179).

Dr. Hubscher received an FY10 Investigator-Initiated Research Award from the SCIRP to pursue these anecdotal clinical findings in a clinically relevant animal model. By testing in a controlled setting using rats with SCI, Dr. Hubscher hopes to determine a potential relationship between step training and bladder control that can inform patient treatment.

To measure the effectiveness of the training on bladder function, Dr. Hubscher and his team are evaluating three groups of rats with severe incomplete SCI; all three groups will be supported by a harness, with the experimental group receiving daily step training with manual assistance, a second group undergoing upper body training with only forepaws on the treadmill, and the control group in the harness without exercise for the duration of the training period. In their initial experiments, significant improvements in bladder function (more efficient emptying of the bladder) with normalized expression of bladder nerve growth factor mRNA levels were found in the step-trained group of animals. Their latest data also suggest that 60 minutes, but not 30 minutes, of step training may attenuate SCI-induced polyuria, an increase in urine production with no change in fluid intake, which the group recently documented in their rat contusion model (Ward PJ and Hubscher CH. 2012. *Journal of Neurotrauma* 29:2490-2498).

Taken together, the urologic benefits of activity-based training could lead to the development of a home-based therapeutic intervention involving a combination of daily step training and drug therapy (targeting bladder neurotrophins such as nerve growth factor, for example) to improve bladder control in individuals with SCI.

Intermittent Hypoxia Elicits Prolonged Restoration of Motor Function in Human Spinal Cord Injury

Gordon Mitchell, Ph.D., University of Wisconsin, Madison

Gillian Muir, D.V.M., Ph.D., University of Saskatchewan

Randy Trumbower, Ph.D., Emory University

SCI disrupts the connections between the brain and spinal cord, leading to lifelong paralysis in Soldiers. However, many SCIs are incomplete, leaving at least some spared neural pathways to the motor neurons that initiate and coordinate movement. Consequently, spinal plasticity can contribute to spontaneous recovery of limb and respiratory function. However, spontaneous recovery is slow, variable, and of limited extent.

Drs. Gordon Mitchell, Gillian Muir, and Randy Trumbower received an FY10 Translational Research Partnership Award from the SCIRP to study the potential value of repeated acute intermittent hypoxia (AIH), alone or in combination with locomotor training, for improving limb function in animals with chronic SCI. They are applying AIH to elicit cellular and synaptic mechanisms of spinal plasticity in non-respiratory motor neurons, and they hope to determine whether it can improve leg function in patients with chronic, incomplete SCI. Preliminary animal experiments have shown that AIH combined with daily training elicits sustained improvement in limb motor function of treated animals with chronic cervical SCI. In addition, preliminary clinical studies revealed a sustained increase in walking speed and distance following a 10-meter walk test and a 6-minute walk test, respectively.

AIH could represent a novel method for stimulating spinal plasticity in individuals with SCI, providing an avenue for controlled restoration of motor neuron excitability, and eventual restoration of volitional movement after incomplete SCI.



Spinal Cord Injury Research Program



Funding research and fostering collaborative environments for the development and translation of more effective strategies to improve the health and well-being of Service members, Veterans, and other individuals with SCI.



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<http://cdmrp.army.mil>

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