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Reeve-Irvine Research Center Publication

Spinal Connections

7th Annual Working 2 Walk Symposium Visits Reeve-Irvine

By Maya Hatch, Ph.D

On November 3rd the Reeve-Irvine Center hosted lab tours for approximately 100 spinal cord injury enthusiasts from around the globe. This tour was the final event on the 3 day Working 2 Walk Symposium agenda, a yearly symposium put on by the Unite 2 Fight Paralysis Foundation, and it was a huge success!

The Unite 2 Fight Paralysis Foundation was founded in 2005 by Susan Maus, Betheny Winkler and Marilyn Smith after they participated in and helped organize the first Rally in Washington on behalf of the SCI community. Fueled from the energy and information gained during this rally, as well as the deep, personal connection each of these women have to the spinal cord injury community, these women founded a very unique advocacy organization. The mission of this foundation is to bring together scientists, clinicians, investors and SCI advocates in hopes to push therapies forward as fast as possible. Each year they have done this by hosting the Working 2 Walk Science & Advocacy Symposium.

Symposium attendees meet and view vendor displays

This year the symposium was held in Irvine, California and featured many of our local SCI researchers including RIRC members, Drs. Leif Havton, Aileen Anderson, Hans Keirstead and Oswald Steward as well as Drs. Mark Tuszynski and Justin Brown from UC San Diego. Other researchers from out of state included Dr. Jerry Silver, who has previously been at our "Meet the Scientists" event, Dr. Ravi Bellamkonda and Dr. Murray Blackmore. In addition to SCI researchers, representatives from InVivo Therapeutics, Acorda Therapeutics and Stem Cells Inc also spoke along with Jonathan Thomas, Chairman of the Independent Citizen's Oversight Committee (ICOC), which is the governing board for the California Institute for Regenerative Medicine (CIRM). Importantly, the symposium also included advocacy speakers Roman Reed, Dennis Tesolat and Bob Yant. This diversity in speakers is what makes this symposium so unique, and what makes the attendees of this meeting so different compared to other symposia. Unlike most symposia where the majority of attendees are other SCI researchers or clinicians, at Working 2 Walk, advocates, family members and individuals from SCI organizations are the majority. This

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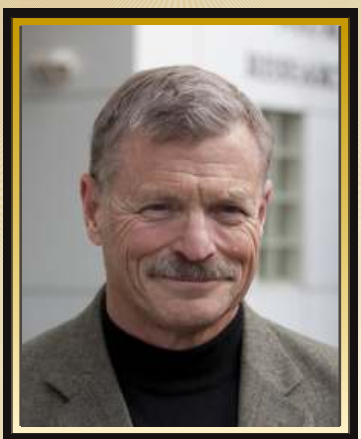

Dr. Oswald Steward

Legislative update: Roman Reed Spinal Cord Injury Research Program remains un-funded:

In the last newsletter, we told you about the efforts to restore funding for the Roman Reed Spinal Cord Injury Research Program of the State of California through Assembly Bill 1657. AB 1657 would have imposed a $1 traffic ticket add-on for moving violations that would have gone into a fund to support spinal cord injury research in the State of California. The bad news is that although the bill passed both the California Assembly and Senate, it was unfortunately vetoed by Governor Brown.

The Roman Reed Spinal Cord Injury Research Program was funded by the California legislature for 10 years (2000-2010). The funding ($1.25 million per year in the past few years) supported a grants program administered by the RIRC that supported a host of novel research projects that have been reported in previous newsletters. This seed funding enabled scientists to gather preliminary data to support grant proposals to NIH and other funding agencies. These seed grants produced approximately $89 million in additional funding—new money for California that not only drives further research but also provides jobs. The University of California provided an additional $1.25 million to keep the program running from 2010-2012, but the failure of AB1657 means that the Program will have to be shut down, at least temporarily.

These seed grants produced approximately $89 million in additional funding—new money for California that not only drives further research but also provides jobs.

We thank Don and Roman Reed and many others for all their hard work in Sacramento, and Assembly member Bob Wieckowski (20th District) for his leadership in introducing AB1657. We are all hopeful that the California legislature and the governor will restore funding to this critical program.

New possibilities for Geron's stem cell program:

In an interesting new development, a company called "BioTime" is making a bid to revive Geron's stem cell program. Geron's stem cell program was put on hold in 2010 as the company chose to direct its efforts toward cancer therapeutics. This decision effectively discontinued the first clinical trial involving human embryonic stem cell therapy for spinal cord injury. Since then, Geron's stem cell program has been "for sale", but no other company has stepped forward until now.

The bid to revive the program brings familiar faces back into the stem cell mix. BioTime is run by Geron Founder Micheal West, who set up "BioTime Acquisition Corp" under Tom Okarma, former CEO of Geron. On November 16, Geron and BioTime announced a letter of intent to go forward with a deal in which BioTime would acquire Geron's intellectual property and other assets related to the human embryonic stem cell program.

It remains to be seen how BioTime will develop the program and whether the discontinued clinical trial for spinal cord injury will be reinstated. There are some hurdles here. For example, the loan that Geron previously received from the California Institute of Regenerative Medicine cannot be reinstated. This loan was specific to Geron. BioTime can compete for funding from CIRM in future grant rounds, however.

Working 2 Walk

Continued from the cover...

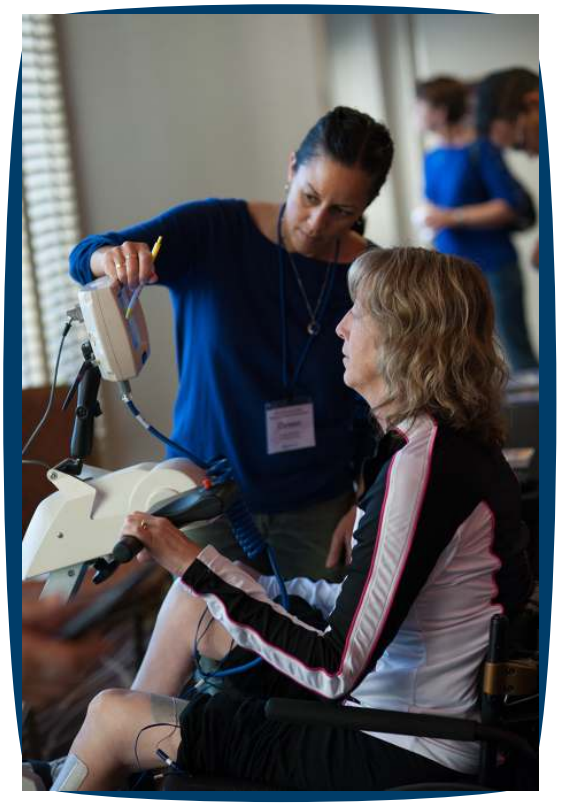
enabled different questions and/or concerns than those typically brought up at other SCI symposia and a different perspective for the researchers, clinicians and investors to consider. Much of this was done during the lengthy breakout sessions at the end of each day; a great addition to the symposium.

The lab tour portion of the symposium at the RIRC was kicked off with Dr. Steward discussing the day-to-day responsibilities of our staff. Attendees then broke off into groups where they were able to visit the various RIRC stations. Drs. Leif Havton, Oswald Steward, Gail Lewandowski and Hans Keirstead answered questions about their research and showed recent data. In the labs, attendees were able to rotate through various stations and learn about how the brain interprets signals, the anatomy of the spinal cord, or cool new imaging machines that we use for research. At the Sue and Bill Gross Stem Cell Center, attendees were able to see, first hand, how our Robo Trunk wheelchair, music glove, Hand & Wrist Assisting Robotic Device (HWARD) as well as other technological tools in our iMOVE lab work (for more information on iMOVE see article in newsletter 20). The day then ended with a box lunch outside in the warm sun.

Overall, the tours and day were a great success and we enjoyed meeting and talking with everyone that participated. This group of attendees was, by far, very different than any of our other tour groups. Everyone from the Working 2 Walk Symposium was very energetic and dedicated to finding and funding a cure for SCI. We, at the RIRC, learned a lot about the questions, concerns and issues this particular group had that were otherwise unknown or not understood. The impact left by this group will stay with many of us for a long time and, in some cases, change our direction and thoughts about the research that we are currently working on.

For more information about the next Working 2 Walk or about Unite 2 Fight Paralysis please visit www.utfp.org. A live blog of the event can be found at http://working2walk2012.wordpress.com/

Joe Bonner demonstrates the functions of a human spinal cord during Reeve-Irvine Research Center laboratory tours



Vendors were available to demonstrate new innovative rehabilitation equipment

Working to Walk Conference

Rehabilitation Corner

By Melissa Pun and Maya Hatch, PhD

The mission of the Reeve-Irvine Research Center is to find new treatments for spinal cord injury through collaborative research and education between scientists and clinicians both at the University of California, Irvine and around the world. Our spinal connections newsletters have served as our conduit to the community exemplifying how we are accomplishing that mission. Additionally the newsletters have also given us the opportunity to educate and inform the SCI community about the basic pathology, relevant scientific terms, or clinical trial information for SCI. To that end, in collaboration with the UCI Physical Medicine and Rehabilitation department at UCI, we would now like to add another section to our newsletter called "Rehabilitation Corner". In each of our newsletters we will either highlight important rehabilitation research going on or provide descriptions/terms related to SCI rehabilitation. To get us started on this new section we have described the basics of SCI rehabilitation below. It is important to note that although we have outlined the ideal or desired rehabilitation strategy for SCI individuals, much of this is determined by a person's medical coverage and/or ability to pay for many of these services.

What is rehabilitation?

Rehabilitation is a treatment or process that facilitates an individuals' recovery to good health and maximizes ability after an injury, illness or disease. The main goal of any rehabilitation is to restore some or all of a person's capabilities (which can be sensory, physical or mental) to his or her highest level of independence. Rehabilitation traditionally utilizes a multidisciplinary approach and a rehabilitation team is usually led by a doctor specializing in physical medicine and rehabilitation (called a "physiatrist"). This team often includes a wide range of experts like physical therapists, occupational therapists, speech therapists, recreational therapists, rehabilitation nurses, neuropsychologists, nutritionists and/or social workers. Due to the multidisciplinary approach, treatments can take place in many different settings ranging from hospitals and rehabilitation facilities to an individual's own home. In addition treatments often involve the combined tools of medications, physical modalities, therapeutic exercise, movement and activity modification, and adaptive equipment and assistive devices such as orthotics (braces) and prosthetics. It is up to the physiatrist to determine which of these tools are needed. Each patient's treatment plan is customized to his or her specialized needs with the primary goal being the prevention of secondary complications and the maximization of residual functionality and reintegration into the community.

Rehabilitation and spinal cord injury

Spinal cord injury (SCI) leads to permanent physical and lifestyle changes, and the goal of rehabilitation after SCI is to help patients and their families adjust to life and optimize the individual's ability to live with as much autonomy as possible. Although there are no current treatments that can cure SCI, rehabilitation strategies have allowed SCI patients to experience improved health with fewer medical complications, increased life expectancy, and shorter hospital stays. Indeed, in some instances rehabilitation has also been shown to improve functional recovery. Therefore, proper rehabilitation has the potential to allow many SCI patients to lead healthy, fulfilling and productive lives within their communities.

The phases of SCI rehabilitation

With SCI patients, no two rehabilitation plans are alike and patients work with their rehabilitation team to develop a plan that incorporates their specific goals. A specialized SCI rehabilitation program typically provides patient-focused rehabilitation services for acute, in-patient and out-patient services that correspond to the acute, subacute and chronic phases of SCI. During the acute management of any SCI patient, the focus is on medical or surgical stabilization. After

An example of a rehabilitation room. Picture courtesy of UCI's physical medicine & rehabilitation department

stabilization a patient's motor level of injury and prognosis for neurologic recovery are assessed. This helps the rehabilitation team determine short and long-term goals.

During the subacute phase (or in-patient services) rehabilitation shifts to helping the patient learn to use their remaining function in an optimal way. In addition to managing medical complications during this phase, physical rehabilitation therapy is initiated where physical therapists work with patients to regain leg and arm strength and drive neural plasticity. This is often done as early as possible after the acute phase and the type of physical rehabilitation varies. For example, some rehabilitation centers are using functional electrical stimulation (FES) therapy to stimulate certain muscles to improve strength and range of motion. Others are using weight supported treadmill training to help improve locomotor recovery after injury. In addition to physical rehabilitation most full scale inpatient rehabilitation programs also include psychologists, occupational therapists, rehabilitation nurses and speech therapists. Occupational therapists help patients relearn fine motor skills essential for daily activities such as eating, grooming, dressing, and bathing. Speech therapists assess patients for any swallowing or speaking difficulties and provide help when needed. Rehabilitation nurses assist with bowel and bladder management if dysfunction exists as well as the prevention and management of pressure ulcers. During the hospital rehabilitation stay, patients may also need to make arrangements for modifications in their home. This includes installing wheelchair accessible ramps to the front door and in the shower. The goal here is to enable the patient to return to as normal a life as possible.

Another important component of the subacute phase is teaching patients about recognizing secondary insults and medical complications such as spasticity, autonomic dysreflexia (AD), or neuropathic pain. Spasticity develops weeks or months after an injury due to amplified and abnormal reflexes and can be treated with certain medications. Autonomic dysreflexia (AD) also develops months, sometimes years after SCI and is an abnormal activation of the autonomic (involuntary) nervous system. AD is often triggered by something that would normally cause pain, but is not perceived by the individual because it is below the level of the injury. AD involves high blood pressure associated with throbbing headaches, profuse sweating, nasal stuffiness, and flushing of the skin. AD can be life-threatening and requires immediate medical attention unless the cause can be immediately identified and eliminated. Neuropathic pain is also commonly experienced by SCI patients. This type of pain is commonly described as a burning or coldness, "pins and needles" sensations, numbness, or itching. Physiatrists may recommend a variety of medications or implantable devices to relieve the pain.

By 1-2 months after injury, the majority of SCI patients are able to live at home. At this time patients can continue rehabilitation through out-patient services on a weekly, monthly or biannual basis depending on their insurance (and/or ability to pay) and the goals set during the in-patient stage. Most out-patient services are focused on continuing physical rehabilitation to improve functional recovery. However, psychological and occupation therapy may continue as well. In addition, vocational therapy is often integrated at this stage. Vocational rehabilitation focuses on evaluating an SCI patient's level of basic work skills and physical and cognitive capabilities necessary for future employment. A vocational rehabilitation specialist will help patients find appropriate employers and workplaces equipped with assistive equipment. For patients that may not be able to return to work, therapists will focus on finding other activities that provide a sense of satisfaction and productivity. This could involve educational classes, hobbies, special interest groups, and participation in family and community events. Another important focus of out-patient rehabilitation is improving a SCI patient's quality of life by reintegration into the community. One way to do this is through recreational activities. Recreation therapy encourages patients to build on their abilities so that they can participate in recreational or athletic activities at their level of mobility. Engaging in recreational activities and athletics helps patients achieve a more balanced and normal life and it also provides opportunities for socialization and self-expression. Consistent physical exercise not only improves patient's quality of life (both mentally and physically) but studies have shown that it may also have beneficial effects on motor and sensory functions. Patients can also attend support groups and hear from other SCI patients, while sharing coping strategies and providing emotional support.

Acquiring a spinal cord injury is a life altering event and proper rehabilitation will enable patient's to live healthy, fulfilling and productive lives. As daunting as the recovery process may seem, a successful SCI rehabilitation team will improve physical and mental functioning, provide emotional support, and help patients successfully reintegrate into the community.

Anatomy 101: Embryonic Stem Cells (ESC), Back to basics

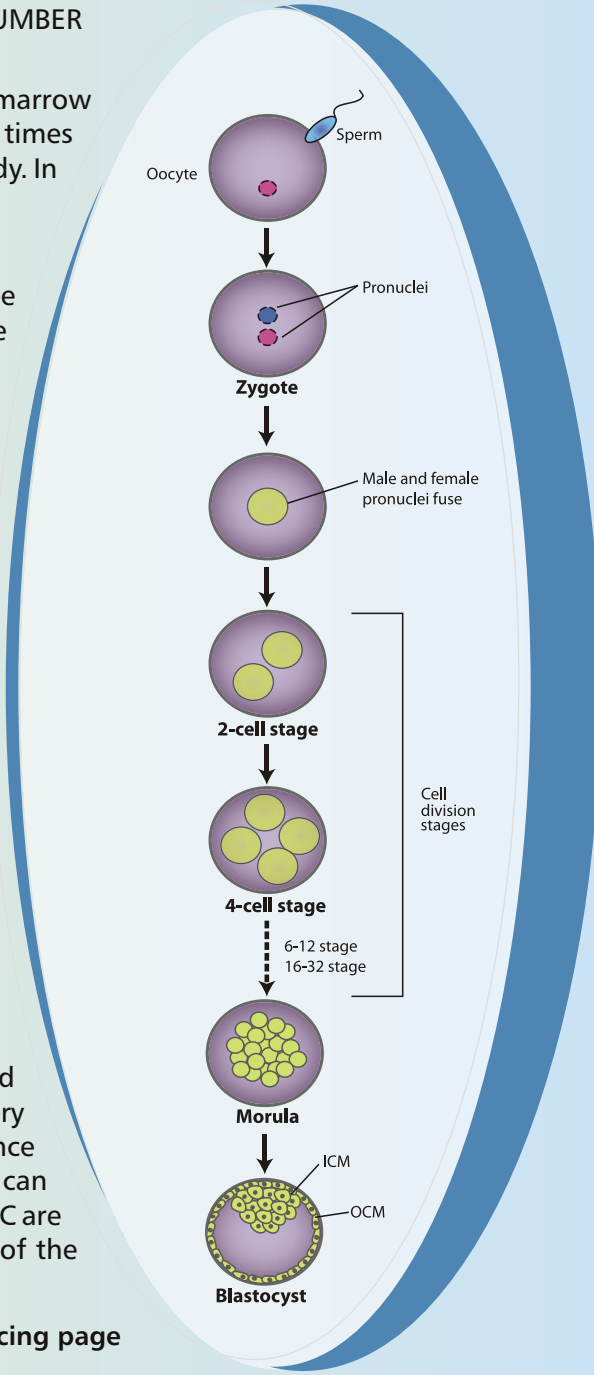
By Maya Hatch, PhD

Stem cell: A general term.

Stem cells are different than the other types of cells in our bodies. To be called a stem cell (SC) a cell must possess two main characteristics: (1) the ability to self renew and make exact copies of itself through cell division and (2) the ability to develop or differentiate into different types of mature cells. This means that to be called a SC a cell does not have a specific identity yet, like for example a liver cell or heart cell. A heart cell is what we would call a mature or differentiated cell. It has a specific function and it doesn't have the ability to divide and renew itself, nor can it become anything else. A heart cell is a heart cell. SCs, however, do not necessarily have the ability to make any type of cell in the body. In fact, only certain types of SC can make ANY cell in the body. Listed below are the 3 general categories of SCs:

1) Totipotent SCs: A cell that can become ALL types of cells in the body, including extraembryonic tissue (such as the placenta).
2) Pluripotent SCs: A cell that can become ALL of the different types of cells in the body, EXCEPT extraembryonic tissue.
3) Multipotent SCs: A cell that can only become a RESTRICTED NUMBER of cell types in the body.

There are a number of different types of SC in the human body (bone marrow stromal SCs, umbilical cord SC, fetal SCs, embryonic SCs) from various times during human development and from various locations throughout the body. In this article we will focus on embryonic stem cells (ESCs).



Oh where, oh where are ESCs from?

When a sperm and an egg come together during fertilization a zygote (see diagram) is formed containing a pronucleus from the sperm (male) and the egg (female). Once these fuse, the first cell of the new organism is established. Over the next few days this cell will go through a series of divisions from a single cell into 2, 4, 6-12, 16-32, and so on. At this stage the solid ball of cells is called a morula. By about 5 days of gestation, the cells of the morula will then reorganize into a fluid filled embryo with an inner cell mass (ICM) and an outer cell mass (OCM), now called the blastocyst. During normal development the blastocyst would attach to the inner membrane of the uterus and pregnancy would be established. If the blastocyst was generated by in vitro fertilization (IVF) it would be implanted into the uterus of the recipient at this age or frozen for later implantation. For research purposes, however, the cells of the ICM are taken and placed in a culture dish that contains specialized media and supplements. The cells of the ICM are ESCs and once plated into a culture dish these cells are the potential start to an ESC line (a number of exact copies of one original SC). The process of generating an ESC line is somewhat tricky and inefficient so not every attempt leads to a useable stem cell line. However, when the line is healthy and established they can divide, multiply and be passaged for a seemingly unlimited amount of time if cultured properly.

Why the fuss over ESCs?

Since ESCs are derived from the very early embryo, or blastocyst as discussed above, they are pluripotent SCs. This makes them very unique, useful and very attractive for biomedical research and potentially for cell-based therapy. Once extracted from a blastocyst and grown in a dish, a very small number of ESC can divide and multiple into millions of ESCs in a very short time. When these ESC are given the right conditions some of them can be differentiated into cells of the central nervous system, while others can be differentiated into skin cells.

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Havton lab takes on a new post-doc

The Havton lab welcomes their newest lab member, Dr. Arthi Amin, as a post-doctoral fellow. Arthi Amin received her graduate training in Philadelphia with Dr. John Houlé at the Spinal Cord Research Center at Drexel University College of Medicine. Her Ph.D. dissertation focused on promoting descending and ascending axonal regeneration after a low thoracic spinal cord injury (SCI). As detailed in our last anatomy 101 section on regeneration (number 21, summer 2012) damaged axons regenerate poorly after SCI due to a variety of factors including formation of the glial scar and lack of trophic or growth factor support. One way to overcome these factors has been to transplant peripheral nerve grafts (PNGs) into the injured cord. PNGs are thought to offer a permissible and growth-promoting environment for injured axons after SCI. Previous work by the Houlé lab showed that injured neurons will extend into PNGs but axons tend to remain within the trophic rich environment of the graft instead of exiting to re-enter host spinal cord tissue. To encourage axonal outgrowth out of the PNGs Dr. Amin first identified which growth factors were present in the PNGs. She then wanted to over-express a combination of growth factors beyond the PNG site in addition to degrading the glial scar hoping to coax axons out of the PNGs and into the host tissue. She found that over-expression of only one neurotrophic factor in combination with degrading the glial scar was not sufficient to increase axonal outgrowth from PNGs but the combination treatment did not cause additional sensory deficits.

Dr. Amin came to the Reeve-Irvine Research Center to work with Dr. Leif Havton to study how the autonomic nervous system is affected after SCI. An injury to the spinal cord affects the micturation reflex (an autonomic spinal cord reflex that initiates urination) and leads to problems of urine storage and voiding. Dr. Amin will study how the coordinated actions between the bladder and bladder sphincters change after SCI. The goal is to develop therapies to treat a condition called bladder-sphincter dyssynergia that often develops after SCI. Normally, when a person voluntarily voids their bladder, the bladder muscle contracts and the bladder sphincter opens to allow urine outflow. In bladder-sphincter dyssynergia, the reflex actions of the bladder become un-coordinated so that there is contraction of the bladder in an attempt to void at the same time that the bladder sphincter is tightly closed (Please see newsletter SC-20 page 9 for more information on dyssynergia).

Dr. Arthi Amin

Currently, Dr. Amin is working on a project in collaboration with Dr. Kornblum and Dr. Novitch at UCLA. After a cauda equina or conus medullaris injury, which represent 20% of SCIs, motoneurons and parasympathetic preganglionic neurons involved in bladder function degenerate. She will use stem cells to replace lost neurons and hopefullly reinnervate the bladder. It is their hope that this treatment will eventually lead to improved bladder function after injury.

Anatomy 101

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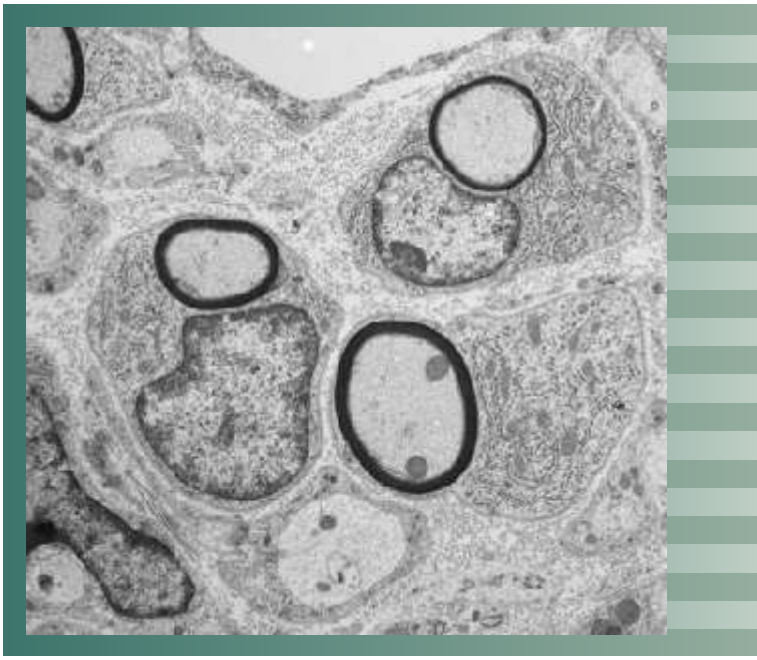
Although ESCs have great promise and reward, they also carry great risk and need to be treated appropriately. Since they are able to make all cells of the body they are also able to become tumors. Additionally, they are very controversial due to the fact that they can only be derived from the early blastocysts and upon removal, the blastocyst is destroyed. However, only extra blastocysts, or those that are going to be discarded after in vitro fertilization, are used. These are often donated for research specifically with informed consent of the donors. Another important distinction to be stated is that these cells are pluripotent, not totipotent, and cannot develop into a fetal or adult organism since they lack the ability to become extraembryonic tissue. Only cells from the morula stage can make both extraembryonic and embryonic tissues.

A NOVEL APPROACH TO REPAIR CONUS MEDULLARIS/ CAUDA EQUINA INJURIES

The Havton laboratory at the Reeve-Irvine Research Center has a particular interest in finding new treatments for the repair of injuries that affect the most caudal portion of the spinal cord, the lumbosacral portion of the spinal cord and the associated nerve roots, the cauda equina. Commonly after traumatic injury to this part of the nervous system, there is extensive damage to the nerve roots. Dr. Havton and his research team has for several years studied the possibility of surgically re-attaching injured nerve roots carrying motor fibers with the spinal cord. However, this would only be possible if a long enough portion of the injured nerve roots remains after the trauma. Other strategies use nerve grafts from other parts of the body to bridge the gap between the spinal cord and severed nerve roots. Although effective, this approach is limited because it sacrifices an otherwise healthy nerve to use for the grafting procedure.

To address this, the Havton laboratory is exploring the use of laboratory-made nerve grafts to replace the need of using the subject's own nerves for bridging material. For this purpose, Dr. Havton and his team have formed a collaborative research partnership with Dr. Kari Christe at UC Davis and Dr. Ahmet Hoke at Johns Hopkins University. The team aims to translate the possible use of biodegradable nerve guidance channels, which have been engineered at Johns Hopkins University in collaboration with Dr. Hoke and Dr. Hai-Quan Mao. This multi-laboratory research team are presently in the midst of exploring whether such biodegradable channels, which may be customized to release growth factors, can stimulate regeneration of nerve fibers from the spinal cord and to the periphery. Initially, the team is exploring the effects of a growth factor called glial-derived neurotrophic factor (GDNF) to encourage regeneration of nerve fibers from motor neurons in the spinal cord. The team has customized several clinically relevant outcome measures, including treadmill walking, skin sensation testing, spinal cord imaging, bladder functional assessments, and electromyography (EMG) of a variety of muscle groups, which have been incorporated into the ongoing studies. If successful, these experimental studies will provide important information for the possible use of engineered channels, which could potentially bridge tissue gaps between the injured spinal cord and nerve roots carrying fibers to muscles.

The ongoing studies by Dr. Havton and his collaborators have recently received the attention and support from the Department of Defense (DoD) and the Congressionally Directed Medical Research Program (CDMRP). Specifically, the research team has been awarded a Translational Research Partnership Award to support studies to explore the feasibility of using GDNF-releasing nanofibers to repair conus medullaris/cauda equina injuries. "*The Department of Defense provides a customized funding mechanism to support collaborative science, which is meant to accelerate progress in the translational research field, and we are very pleased to receive this excellent support* ", states Dr. Havton. In August, 2012, Drs. Havton, Christe, and Hške participated in the Military Health System Research Symposium in Fort Lauderdale, Florida, where the research team also presented new research data from the project. The theme of the four-day conference was "Military medical research across the continuum of care" and included many oral podium and poster presentations related to trauma research. "*It was an excellent experience to be part of the symposium in Fort Lauderdale, and progress that is being made by the several projects that are currently funded by the Department of Defense will clearly benefit the care of both military-related and civilian forms of spinal cord injury*", concluded Dr. Havton.



Electron microscopic image of regenerating nerve fibers inside a nanofiber guide tube, which has been surgically placed into the spinal cord in a cauda equina injury model. The nanofiber releases GDNF, a growth factor, which may encourage motor axons to grow.

Dr. Catherine Cahill joins RIRC

In August, 2012, Dr. Catherine Cahill joined the UC Irvine School of Medicine as Associate Professor of Anesthesiology & Perioperative Care and also became the newest member of the Reeve Irvine Research Center. Dr. Cahill comes to us from the Department of Pharmacology & Toxicology in the Faculty of Health Sciences at Queen's University, Kingston Ontario.

Dr. Cahill's research program explores mechanisms underlying neuropathic pain, a common consequence of spinal cord injury. Neuropathic pain is a chronic pain that cannot be associated with an identifiable painful stimulus. Neuropathic pain is very common in people who have suffered a spinal cord injury with some studies showing incidence greater than 80%. The impact of this pain in spinal cord injury patients is exemplified by statements from patients indicating that resolving their pain is more important than being able to walk. Ample evidence indicates that neuropathic pain impairs patients' mood, quality of life, activities of daily living, and performance at work.

Standard pain medications are often not effective for neuropathic pain. Even strong opiates are sometimes ineffective, and also have adverse side effects, including sedation, tolerance, physical dependence, and hyperalgesia. The goal of Dr. Cahill's research is to identify the neural mechanisms to neuropathic pain with the ultimate goal of developing novel and more effective treatments. In addition, as we identify new ways to improve function after SCI, it is important to be sure that novel strategies aimed at improving motor function do not have adverse effect of increasing pain.

Dr. Cahill's laboratory uses well-characterized animal models of neuropathic pain and explores changes in brain circuitry that may be responsible for pain. Behavioral tests are used to assess allodynia – pain to a stimulus not normally painful, and hyperalgesia – exaggerated response to a normally painful stimulus. Changes in brain circuitry are assessed using biochemical and neuroanatomical techniques (light and electron microscopy) to investigate neuronal-glial interactions and factors released from glia that contribute to synaptic plasticity. A particular focus is on changes in G-protein coupled receptor trafficking that may relate to the development of neuropathic pain. In addition, as a neuropharmacologist, specializing in opioid pharmacology, she has been validating the delta opioid receptor as a target for novel treatments for chronic pain, as well as investigating the mechanisms underlying the analgesic effects of ultralow dose opioid and alpha adrenergic antagonists in neuropathic pain conditions.

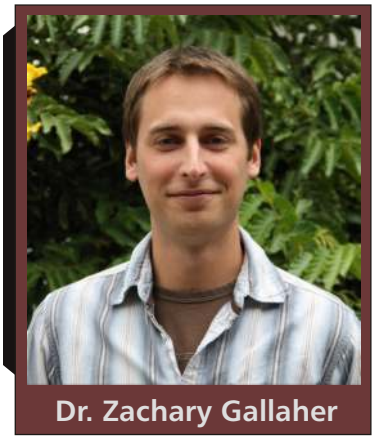
Dr. Cahill received her B.Sc. in Chemistry from Mount Allison University in 1987, and her MSc and PhD in Pharmacology from Dalhousie University in 1992 and 1996. Her doctoral dissertation was on the role of adenosine in opioid analgesia. Dr. Cahill received a Medical Research Council Postdoctoral Fellow (1996-1998) to study under the supervision of Drs. Andy Dray and Terence Coderre in the Pain Mechanisms laboratory at the Clinical Research Institute of Montreal. There she investigated the impact of the immune system in chronic pain and was involved in various collaborative studies within the McGill Pain Research Centre. Dr. Cahill received the first Ronald Melzack Pain Research Award to study with Dr. Alain Beaudet in the Department of Neurology and Neurosurgery at the Montreal Neurological Institute from 1998 to 2001. Her research in the Beaudet laboratory was the first to demonstrate that trafficking of one G-protein coupled receptor subtype is regulated by the activation of another receptor subtype from the same family. Dr. Cahill joined the Department of Pharmacology & Toxicology in the Faculty of Health Sciences at Queen's University, Kingston Ontario as an Assistant Professor in 2002, with a cross-appointment in the Department of Anesthesiology & Perioperative Medicine. There she received multiple awards including a Canada Research Chair in Chronic Pain, a Premier's Research Excellence Award, the Basmajian Award for Excellence in Biomedical Research, a Pfizer Neuropathic Pain Research Award and the Merck Junior Scientist Award from the Canadian Pharmacology and Therapeutics Society.

The Cahill laboratory has collaborations with multiple laboratories in Canada and the United States. Her laboratory is currently funded by the Canadian Institutes of Health Research, Pfizer Canada.

The RIRC is pleased to welcome Drs. Joseph Bonner and Zachary Gallaher who have joined Dr. Oswald Steward's lab as postdoctoral fellows. Dr. Bonner comes to us all the way from "the city of brotherly love" in Pennsylvania, Philadelphia, and Dr. Gallaher has traveled down from beautiful Washington State. Please join us in welcoming two new members to the RIRC family!

A Warm Welcome from RIRC

Dr. Gallaher received his PhD from Washington State University under the mentorship of Dr. Krzysztof Czaja. The Czaja laboratory is one of the few in the world investigating the potential for the peripheral nervous system (PNS) to generate new neurons following injury. Dr. Gallaher's thesis work investigated the ability of cells within a particular structure in the adult rat PNS, the dorsal root ganglia (DRG), to proliferate.

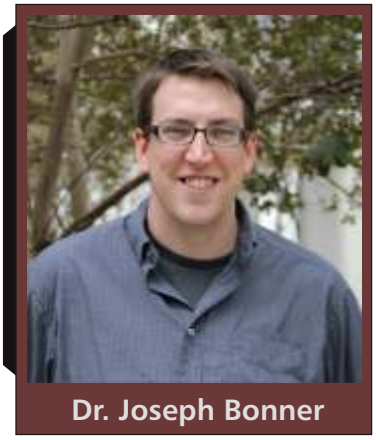


Dr. Zachary Gallaher

The PNS consists of nerves that connect your limbs and organs to the brain and spinal cord, collectively called the central nervous system. Being without a protective casing of bone, the nerves of the PNS are increasingly vulnerable to mechanical injuries and toxic insults. Although these nerves have some capacity to regenerate, damage is sometimes so severe that neurons die off, making the generation of new neurons necessary for functional recovery.

In his thesis work, Dr. Gallaher induced DRG neuronal death using high doses of capsaicin, the chemical that makes chili peppers hot, to study their ability to proliferate and regenerate. His work showed that about half of these neurons are sensitive to capsaicin and will die after exposure to a high dose. Interestingly, the number of neurons in the DRG recovered in just sixty days. When trying to determine the source of this neuronal restoration, Dr. Gallaher and his mentor found increased proliferation of a population of supportive cells called satellite glial cells. These cells may be the source of the recovery in neuronal numbers but further work is necessary to determine if this is true. The knowledge gained from this work is not only informative for peripheral nerve injuries but it will also be useful for other injuries like spinal cord injury, traumatic brain injury, or other injuries that display neuronal loss.

Dr. Bonner comes to us from the Drexel University College of Medicine where he completed his doctoral thesis with Dr. Itzhak Fischer. Dr. Fischer is an expert in the fields of neural stem cell biology and cell transplantation in animal models of spinal cord injury. While at Drexel, Dr. Bonner studied the ability of neural stem cell transplants to integrate into the injured spinal cord and act as a relay to restore hind limb sensory input.



Dr. Joseph Bonner

In the healthy spinal cord, neurons and their axons (see page 8 of newsletter 21 for a definition) carry signals from the brain to the body enabling movement and sensation. For example, when a person wants to grab an object, the thought initiates a signal (within neurons) in the brain. This signal then travels to the spinal cord where other neurons are present to receive the signal. Once these neurons (target neurons) receive the signal, they transmit the information to hand or finger muscles telling them to grab. During a spinal cord injury many of these neurons and axons are damaged causing this long distance communication to be interrupted. In addition the injured neurons are unable to efficiently re-grow and make the new connections on target neurons needed to restore proper function. In hopes to repair this connection relay models of spinal cord injury repair have been introduced where a new neuron is placed in between the injured neuron and the target neuron. This new neuron is able to complete the brain-to-body circuit and hopefully restore long distance communication. This method has the advantage of removing the difficult task of growing a new, long axon from the injured neuron and giving that job to a new, healthy neuron that is inherently more suited for making those long

Continued on facing page

Welcome

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Dr. Zachary Gallaher

In joining Dr. Steward's lab, Dr. Gallaher will be bringing a new element to the lab's PTEN team. As mentioned in other newsletters, Dr. Steward's lab and collaborators at Harvard and UCSD have shown that suppression of PTEN results in significant regeneration past the spinal cord injury site. Using his expertise in the PNS, Dr. Gallaher's project will determine if suppression of PTEN similarly enhances the regenerative capacity of peripheral spinal nerves following nerve damage. This work is of great importance given that approximately 800,000 Americans experience some form of nerve damage each year and that 20% of SCIs involve damage to the cauda equina, a bundle of nerves traveling inside the spinal column of the lower back that control function of the bladder, bowel and lower limbs.

Dr. Joseph Bonner

connections. The disadvantage is that this new neuronal circuit may not be able to function as effectively as the original circuit. In his thesis work Dr. Bonner, together with his mentor and collaborators at Drexel, was able to show that the relay method of repair restored some ability of the spinal cord to transmit sensory information from the hind paw, although it was unclear if the animals were able to use this restored input in a meaningful way. This finding demonstrates that the relay is a technically feasibly method of repair but will require more research to reach full efficacy.

In joining the Steward lab, Dr. Bonner will be determining if this relay method of repair can be applied to systems other than sensory tracts. He has received a 2-year fellowship from the Craig H. Neilsen foundation to examine if a neuronal relay can be established between the injured corticospinal tract (which controls voluntary movement) and motor neurons (which drive muscles) below the level of the injury. This project will combine the expertise of Dr. Bonner (neural stem cell transplantation) and the Steward Lab (corticospinal tract repair, and recovery of function) and hopefully provide a useful advance in the study of spinal cord injury repair with neural stem cells.

Reeve-Irvine Research Center

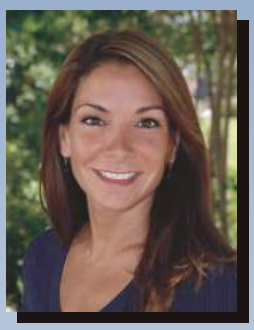
For questions regarding our educational and scientific programs or general information on the Reeve-Irvine Research Center, please contact:

Kelli Sharp, DPT
sci@uci.edu
949-824-5145

Interested in fundraising or making a donation?

Please contact:

Tania Jope
tania.jope@uci.edu
949-824-5925



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University of California, Irvine
2107 Gillespie Neuroscience Research Facility
Irvine, CA 92697-4292
945-824-5739
www.reeve.uci.edu

Anatomy 101: NSCs: What are they and what can they do?

By Maya Hatch, PhD

In the past year there has been a lot of buzz about the start of the second stem cell based trial, and the first neural stem cell (NSC) transplant, in spinal cord injury (SCI). Now that the first cohort of patients from Stem Cells Inc. has been successfully transplanted with NSC's, and the second cohort of patients with incomplete injuries is to be started, we thought it would be beneficial to define what NSC are, how they differ from embryonic stem cells (ESC's; please refer to Anatomy 101 article on ESC on page 6) and what they are capable of in regards to SCI.

Neural stem cells (NSCs)

Neural stem cells are just as their name suggests; they are stem cells that are already specified to a neural lineage. So what does that mean exactly? They are stem cells so, as we mentioned in the ESC anatomy 101 article, they are able to continually self renew and can be differentiated into mature cells. The difference between NSCs and ESCs is that NSCs are multipotent and can only be differentiated into a restricted number of mature cells. Specifically, NSCs can only make cells of the nervous system; astrocytes, oligodendrocytes and neurons. Therefore, in simplistic terms, NSCs are cells that can continuously self renew but they can only give rise to astrocytes, oligodendrocytes or neurons.

The origin of NSCs

During early human development NSCs arise from specific cells, called neuroepithelial cells, that line the neural tube. As we mention on page 12, when a sperm fertilizes an egg a zygote is formed. This zygote then divides and ultimately forms the blastocyst. Around 2-3 weeks after fertilization, and after the implantation in the uterus, the blastocyst goes through a series of folds and is reorganized into three germ layers*. These layers ultimately give rise to all of the tissues and structures of the human body. One of the layers, the ectoderm, gives rise to the skin, nails, hair, eyes and ears, and the nervous systems. The outer part of the ectoderm will be further subdivided and this is where the neural tube will be formed. The neural tube gives rise to all of the cells of the central nervous system and the cells that line this structure produce the first NSCs.

Much later during development (after 12 weeks or so) the brain develops and a secondary site for NSCs exists. This area is called the subventricular zone (SVZ) and it lines the lateral ventricles, a structure that hugs the hippocampus in both hemispheres of the brain. Although brain anatomy is complicated, all you really need to know is that there exists a pool of NSCs in the SVZ of the brain after development, and they exist in late stage embryos, the fetus and throughout adulthood. Although all NSCs by definition should be able to give rise to any type of neuron or glial cell (yes, there are multiple types of neurons and glia), it is believed that NSCs from younger or earlier stages of development will divide more extensively and tend to have more multipotentiality. Recent studies have also shown that there is a small pool of NSCs in the spinal cord as well.

Stem cells from the neural tube and the SVZ are the natural or original origin of NSCs and these cells can be dissected from these areas and used in transplantation studies. However, NSCs can also be produced and grown in the lab from other sources. ESCs can be differentiated into NSCs within a culture dish if certain media, supplements and growth conditions are provided to the ESCs. NSCs can also be produced from a process called direct reprogramming. Unlike ESCs that arise from the inner cell mass cells of blastocysts, SCs can be "artificially" derived through a process called reprogramming (please see spinal connections number 17, 2010, page 9 for more info). This process forces an adult skin cell or fibroblast back into its SC state (or back into a NSC) by the addition of certain factors that will turn on specific genes and program the cell to become something new.

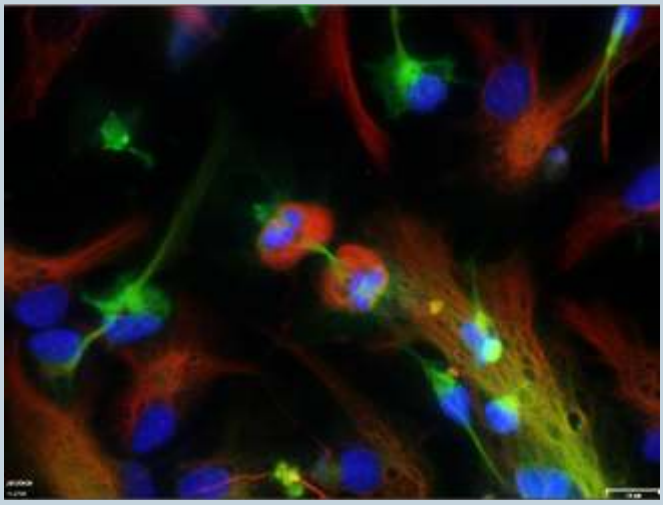
The NSCs being used in the Stem Cells Inc. trial (HuCNS-SC) were derived from the brain and spinal cord of human fetuses at a fairly young stage. Key markers that NSCs express were then used to select and separate the NSCs from other cell types they did not want. These HuCNS-SC were then expanded and grown in culture for a short time prior to being prepared for transplantation. These were the cells used by Drs. Aileen Anderson and Brian Cummings in their proof-of-concept experiments.

NSC for spinal cord repair, what can they do?

A SCI results in para- or tetraplegia, depending on the level of the injury, as well sensory and autonomic dysfunction. This loss of function or dysfunction is permanent and the adult spinal cord is unable to significantly repair itself. After an SCI a number of things occur. Notably, cells of the CNS like oligodendrocytes and neurons are

lost, detrimental/toxic compounds are released, axons and spinal cord tissue can be severed, cut or lost, and a large cavitation and scar can form leaving a large, impenetrable area. All of these play a role in the dysfunction seen after SCI. Many believe that NSC transplants can be a very successful therapeutic intervention because they are able to differentiate into neurons, astrocytes and oligodendrocytes, all the cells needed to reconstitute or repair the spinal cord. So what can these three cells do exactly?

Death of oligodendrocytes due to the injury can result in the loss of the myelin sheath that they provide to axons. Myelin, which behaves like insulation around a wire, protects axons and enables quick propagation of a signal down the axon so that signals from the brain are relayed quickly to the rest of the body. When axons lose their myelin (become demyelinated), they lose the ability to transmit action potentials and this contributes to autonomic, sensory and locomotor deficits after SCI (please see our spring 2005 newsletter for more info and a diagram of myelin). The demyelination of axons also leaves the now naked axon vulnerable to detrimental compounds or cells in the CNS, creating an unhealthy axon. The replacement of oligodendrocytes from the NSC transplant can provide a new pool of oligodendrocytes that are able to re-wrap (or remyelinate) axons and potentially restore axonal transmission.



Stem Cells Inc. NSCs in culture
Courtesy of Dr. Aileen Anderson

In addition to the unhealthy axons left from demyelination, axons themselves can be damaged or cut as a result of an SCI. This can leave a break or severing of communication between axons from one side of the injury to the other. This is another reason that signals may not be relayed correctly from the brain to the rest of the body. A new source of neurons, provided by the NSC transplants, may be able to mature and extend their axons to create a bridge of communication between the two sides, and therefore reconstitute proper neuronal transmission. These transplanted neurons may also be able to support the survival and extension of surviving neurons and axons already present in the spinal cord.

Astrocytes, on the other hand, are not extensively lost during an SCI. Instead, they tend to form a barrier (the scar) between the damaged injury site and the rest of the spinal cord tissue. This is meant to be helpful by separating undamaged and damaged tissue, but it also creates a problem. For example, these damaged astrocytes can also secrete detrimental compounds as a result of the SCI, making repair difficult. The scar also prevents axonal regrowth in that area. Some NSC transplants will mature into astrocytes. These transplanted astrocytes tend to be younger than those left in the spinal cord and they can provide supportive compounds, such as growth factors, to the injury site. These growth factors can help support the growth, maturation and function of other transplanted cells (like the oligodendrocytes) as well as be supportive to the damaged axons and cells remaining in the spinal cord.

Here we have mentioned only some of the ways that NSCs transplants can be beneficial to SCI. Although many animal studies on NSC transplants have been done and their potential as a therapy for SCI is great, their safety in human SCI is still largely unknown. Additionally, their full capability to restore locomotion and/or other sensory and autonomic functions is still being investigated. With the current Stem Cells Inc. trial using the HuCNS-SC cells well underway and in the second cohort of patients, hopefully we will soon be able to answer the question of what these cells really can do for SCI.

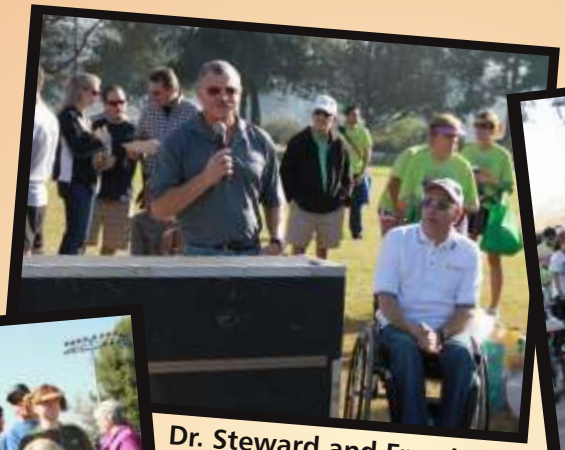
* The three germ layers are the endoderm, mesoderm and the ectoderm. The endodermal layer forms the GI tract, the respiratory tract, endocrine glands, the urinary system and the auditory system. The mesodermal layer gives rise to the muscles, bones, blood and blood vessels, the lymphatic system, the circulatory system and connective tissue.

Tara Llanes, former professional downhill mountain bike racer, has been raising funds for the RIRC for years and has raised over $40,000 to support SCI research. Each year her event continues to bring in new racers and sponsors and create a huge buzz amongst cyclists. The energy of this event is truly energizing. The Reeve-Irvine Research Center would like to say a special thanks to Tara and her team of volunteers as well as to the Northstar Resort and a long list of sponsors. Please look out for her event each fall. We announce her events on the Reeve-Irvine web site reeve.uci.edu and you can also follow it on the Race for Tara site tarallanesclassic.org/. The Tara Llanes Classic is an event you don't want to miss!

Never Give Up is Tara Llanes' Motto

Dr. Oswald Steward, Tania Jope and Tristan Steward represent the RIRC with Tara Llanes

Plymouth Rock N' Run North Orange County



Dr. Steward and Fran Lopes give thanks

They're off!

Kid costume winners and 1K runners

All of us at the Reeve-Irvine Research Center would like to give sincere thanks to the Plymouth Rock N Run Team for their continued support and for all their hard work and dedication. A special thanks to the sponsors who supported the event, the community volunteers and to Research for Cure for their guidance. There is no better way to spend the Thanksgiving holiday than to give back. We are grateful to all the racers for the record turn out this year, a record high 2000 runners participated! Way to go Plymouth Rock N Run!

PLANNED GIVING

Are you considering including Reeve-Irvine in your estate plans?
Your planned gift can help create tomorrow's cures.

For information please contact:
Tania Jope, Director of Community Development
(949) 824-5925 or email tania.jope@uci.edu

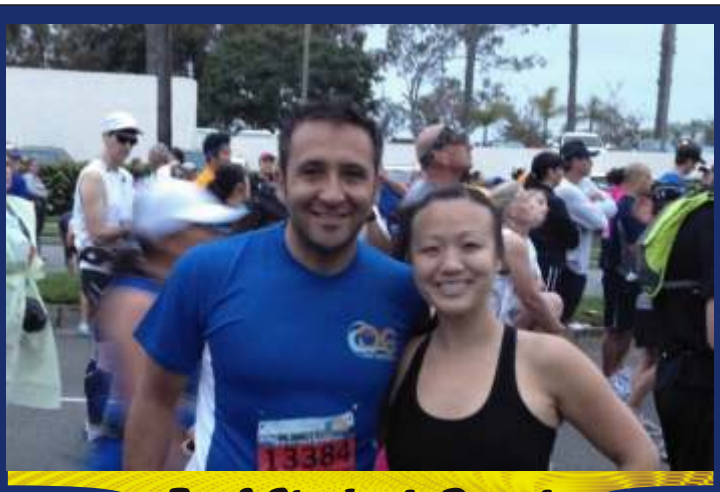
A shining example of how to raise funds

Tan Rezaei does it again! In the Summer 2008 issue of the Spinal Connections newsletter we featured an article on Tan Rezaei who ran a marathon in honor of his dear friend Bill Chiou, who was injured in a surfing accident. Tan was able to raise thousands by asking his friends to support his run an Orange County marathon. All of the money he raised was sent to the Reeve-Irvine Research Center. This year Tan invited his fiance Stephanie Chew to join him in another half marathon to support the RIRC in the name of Bill Chiou. In a short time the two were able to rally friends and family to support their effort. It was a great success!! When asked about their run Tan and Stephanie said,

"*We both believe in the mission and vision of the scientists at the Reeve Irvine Research Center. The devotion of the Reeve-Irvine Research Center's scientists to find new treatments for spinal cord injury is exciting and inspiring. The RIRC creates a possibility of treatment for our friends and community members and we're honored to be part of this wonderful mission in any way we can contribute*".

On October 6th Tan and Stephanie Rezaei were married in Palos Verdes, CA. All of us at the Reeve-Irvine Research Center would like to thank them for their compassion and generosity and congratulate them on their marriage!

As many of you are aware, a huge obstacle in our ability to carry out cutting edge research in a timely manner is lack of funding. More and more government funds are dwindling and harder to secure. Also, when we launch innovative projects, preliminary data is a pre-requisite to receiving federal grants. Where do the funds for these new ideas come from? They come from you, the private donor. Private gifts enable researchers to explore new ideas and help create preliminary data that would otherwise go undiscovered. No matter how small, every bit that you do to help support the Reeve-Irvine Research Center is important.



Tan & Stephanie Rezaei

We understand that not everyone has access to 501(c) 3 organizations and personal donations are difficult. We were all been hit by the recent downturn of the economy. But there are other ways you can help. One simple way to help out is by participating in a run to support research. It is a great way to raise money and get some exercise!

If you are interested raising funds or doing a run to support research, please contact Tania Jope at (949) 824-5925 or tania.jope@uci.edu.

RIRC THE REEVE–IRVINE RESEARCH CENTER

The Annual
CALIFORNIA SPINAL CORD INJURY "MEET THE SCIENTISTS" FORUM
Saturday, March 16, 2013

William J. Gillespie Neuroscience Research Facility University of California, Irvine

The California Spinal Cord Injury "Meet the Scientists" Forum brings together scientists, researchers, clinicians, associates & students from the RIRC, UCI and beyond.

The Forum gives individuals from the SCI community the opportunity to meet scientists directly, ask questions, and get a sense of SCI research today.

If you have any questions, don't hesitate to contact:

Tania Jope
tania.jope@uci.edu
949-824-5925

Ways to Give....

Since there are a variety of ways one can support the Reeve-Irvine Research Center at the University of California, Irvine, it's important you choose the options that are most appropriate for you. Planned giving enables a donor to arrange charitable contributions in ways that maximize his or her personal objectives while minimizing the after-tax cost. Listed below are just a few ways to send your gift to support the critical spinal cord injury research happening today and in years to come.

Should you have questions or if you would like to receive more information on giving, please contact

Tania Jope
(949) 824-5925 or tania.jope@uci.edu.

Those wishing to make a donation directly may send checks payable to the UCI Foundation/Reeve-Irvine to the address below:

Tania Jope,
Director of Community Development
Reeve-Irvine Research Center
University of California, Irvine
2107 GNRF
Irvine, CA 92620-4292

Or donate on line by visiting our website at
www.reeve.uci.edu

Check out our website!

We would like to say a special thanks to Shad Davis a personal friend of Roman Reed for donating his time to update our website!

Thank you Shad!

www.reeve.uci.edu

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Monthly Lab Tours

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Study to understand trunk stability and control.

- Subjects with spinal cord injury will receive trunk stability testing.
- The session will be held in Irvine on the UC Irvine campus.
- Participants will receive **$10.00** for completing each session.
  3 session minimum. 10 session maximum.
- If your SCI occurred **at least 1 year ago** you may be eligible.

All personal information will be kept confidential.

If interested, contact Kelli Sharp, DPT
sci@uci.edu or call (949) 824-5145