

# Spinal Connections

Reeve-Irvine Research Center Publication

## *Reeve-Irvine Research Medal Awards*

Christopher Reeve's spirit after his tragic injury, and worked with UC Irvine to establish a spinal cord injury research center in Christopher's name. Starting with her lead gift of one million dollars, the Reeve-Irvine Research Center has evolved into the world-class research facility that it is today.

Concurrent with the founding of the Reeve-Irvine Research Center Joan Irvine-Smith established an annual award for research in spinal cord injury, originally named the "Christopher Reeve Medal", and later renamed the "Reeve-Irvine Research Medal" in 2003 with Christopher's approval.

The Reeve-Irvine Research Medal recognizes an individual, or individuals, who have made highly meritorious scientific contributions in the area of spinal cord injury repair; and whose research has stood the test of time and scrutiny. The medal includes a \$50,000 cash award generously provided by the Joan Irvine-Smith and Athalie R. Clark Foundation. Their kindness has made it possible to continue to recognize the work of pioneering investigators whose work has brought us closer to cures for afflictions affecting the spinal cord. Between 1996 and 2012 twenty three exceptional researchers have received this prestigious award.

The latest recipients of the Reeve-Irvine Research Medal are Michael Beattie and Jacqueline Bresnahan, both from the Department of Neurosurgery at the University of California, San Francisco. The award was celebrated by a scientific symposium, which was held at the Newkirk Alumni Center on the UCI Campus.

Michael Beattie graduated from the University of California, Davis with a B.S. in Biological Psychology, and received his

Ph.D. in Neuropsychology and Neuroanatomy from Ohio State University. He did his postdoctoral work at Ohio State and Michigan State University. From 1979 until 2006, he was Assistant, Associate, and Full professor at Ohio State University. He helped form the department of Neuroscience, and was Chair of the department from 1999 until 2006. He also served as the director of the Neuroscience Graduate program and held the Brumbaugh Chair in Neuroscience

Joan Irvine-Smith, a well known Californian and philanthropist, played a lead role in establishing what is now the University of California, Irvine. In 1996, she was inspired by



*On behalf of the Joan Irvine Smith & Athalie R. Clarke Foundation  
James & Madeline Swinden and Mary Anne Smith alongside  
Dr. Steward, Director of the Reeve-Irvine Research Center,  
present the 2012 Reeve-Irvine Research Medal Award  
to Dr. Michael Beattie and Dr. Jacqueline Bresnahan*



Dr. Oswald Steward

## *A Fond Farewell to Shorty*

We are sad to report that Suzanne Mae Short of Laguna Beach, California passed away January 12, 2013 at the young age of 51. Suzanne, known to her friends as "Shorty", was a long time friend and supporter of the Reeve-Irvine Research Center.

Suzanne grew up in Indianapolis, Ohio and majored in architectural drafting at Indiana University. During her junior year, she was hit by a drunk driver leaving her a quadriplegic. After years of rehabilitation she finally settled in Laguna Beach California where she worked on becoming an artist. With help from her architectural background, and her positive attitude, she soon became a gifted mouth artist. Her expertise was water colored portraits of pets and children. She even did portraits of Ted

Danson and Woody Harrelson, actors from her favorite television show "Cheers", which she later had the opportunity to present to each actor personally. In 2006, Anchorman Ed Bradley of 60 Minutes conducted an interview at the Reeve-Irvine Research Center with Suzanne, and after the interview Suzanne presented Ed Bradley with a portrait of himself that she had created. This was one of Ed Bradley's last interviews before his passing.

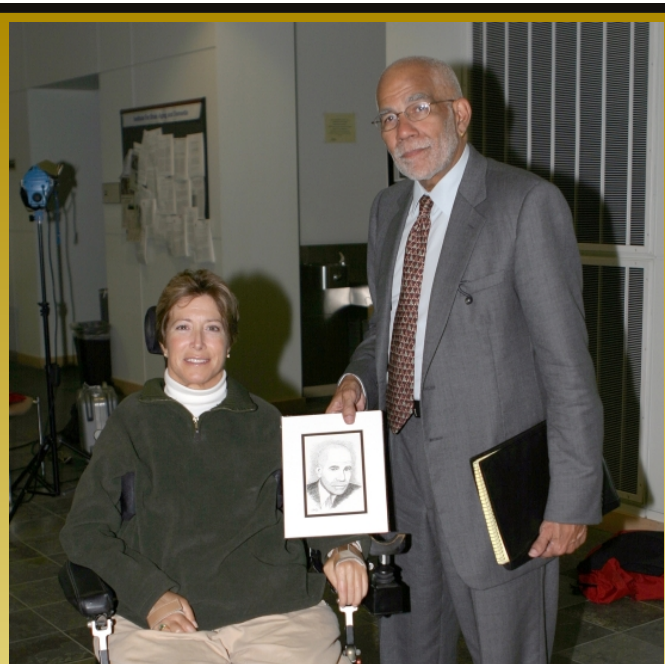
Suzanne's gift of art was appreciated by so many. She was a featured artist at the Laguna Beach Sawdust Festival, which includes some of Laguna's top artists, and she was featured in an article in the LA Times for her talent. At her funeral at Laguna Beach United Methodist Church on Friday, January 18 many stories of her great humor, generosity and kindness were told.

Suzanne's contributions to the Center were invaluable and she has left us all with a lasting impression of strength, perseverance and hope. All of us at the RIRC will sorely miss her and she will always be remembered for her positive attitude, vibrant spirit, incredible talent and her zest for life.

Our hearts go out to her family, friends and anyone else who had the chance to know her.

## In this issue...

Cahill Lab Update	Pg 3
Z. David Luo, M.D., Ph.D.	Pg 4
PTEN	Pg 5
Havton Lab Update	Pg 6
Anatomy 101	Pgs 8-9,10-11
Dr Camelia Danilov	Pg 12
Weinberger Award	Pg 13
BCI Buzz	Pg 15



Anchorman Ed Bradley of 60 Minutes visits the Reeve-Irvine Research Center for one of his last interviews before passing. During his visit Suzanne Short was interviewed and presented Ed Bradley with a portrait of himself.

## Cahill Laboratory Update

Dr. Catherine Cahill is a recent addition to the RIRC and, as mentioned in the last newsletter (number 22, winter 2012), her research explores the underlying mechanisms of neuropathic pain, a common problem in many individuals with spinal cord injuries. One treatment for such pain involves opiate drugs, but these are problematic for several reasons. Earlier this year Dr. Cahill and her colleagues published a paper in the high profile journal "Nature Neuroscience" revealing new insights into the mechanisms for some of the negative effects of opiates.

Opiates, like morphine, are powerful drugs either synthetically made or naturally derived from the poppy plant. These opiates can be extremely successful in relieving pain, yet consistent use of them can lead to the development of tolerance as well as a phenomenon called "hyperalgesia". Tolerance is the progressive lack of response (or potency) of a drug like morphine after repeated administration. As tolerance develops in individuals, physicians often increase the opioid dose in order to achieve the same analgesic (pain relieving) effects. In some people, continued high dose opioid use can lead to hyperalgesia in which there is paradoxical hypersensitivity to pain. In this condition, rather than reducing pain, opioids actually cause pain. Although the development of tolerance and hyperalgesia seem to reflect opposing processes, the commonly held view in the field until now was that they arise from similar underlying cellular and molecular mechanisms. Dr. Cahill's paper breaks new ground by showing that there are mechanistic differences between tolerance and hyperalgesia.

Dr. Cahill and colleagues demonstrated that opioid-induced hyperalgesia (but not opioid tolerance) is due to the activation of cells in the spinal cord called microglia. Once activated by morphine, the microglia release a protein called brain derived neurotrophic factor (BDNF), which then acts on pain specific neurons causing them to be more active. The paper goes on to dissect the details of the mechanistic cascade and mediators involved, revealing new potential targets for therapy. The paper also found that very low doses of the opioid antagonist, naloxone, can prevent the development of opioid-induced hyperalgesia. This is an important discovery for patients with chronic pain that are regularly treated with morphine.

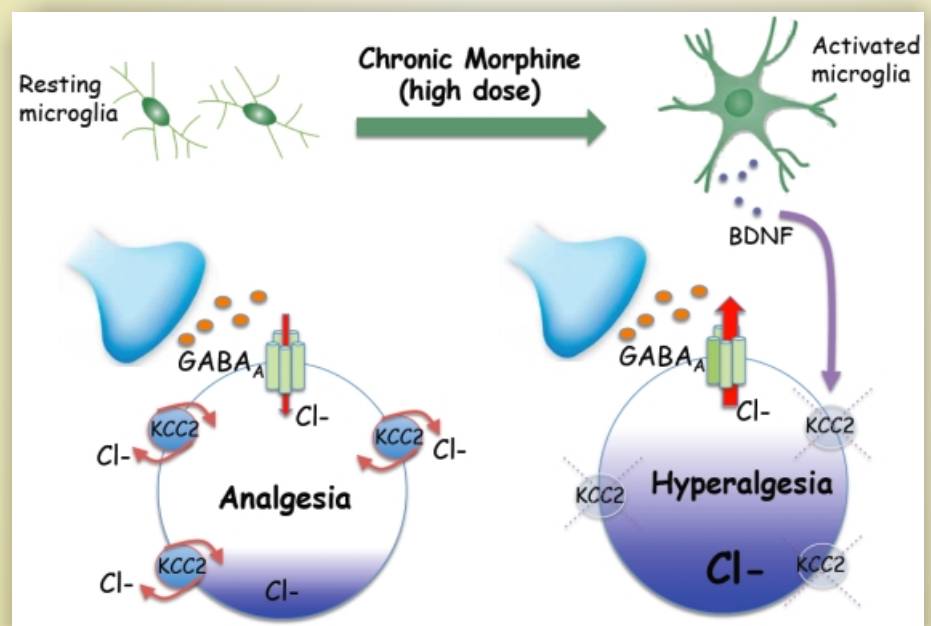


Diagram of how chronic morphine acts on lamina 1 neurons in the spinal cord. Diagram courtesy of Dr. Catherine Cahill

Similar mechanisms may also contribute to the development of chronic neuropathic pain conditions (see the Anatomy 101 section in newsletter 13 for more information on neuropathic pain), from which many spinal cord injured patients suffer. This mechanistic overlap suggests the novel idea that naloxone may also help in neuropathic pain conditions, although more experiments would need to be performed to confirm that. Dr. Cahill's paper is important for the field because now that we understand how opioids can cause pain, pharmacological interventions to prevent this intolerable side effect can be pursued and possibly translated into other pain conditions with similar etiology.



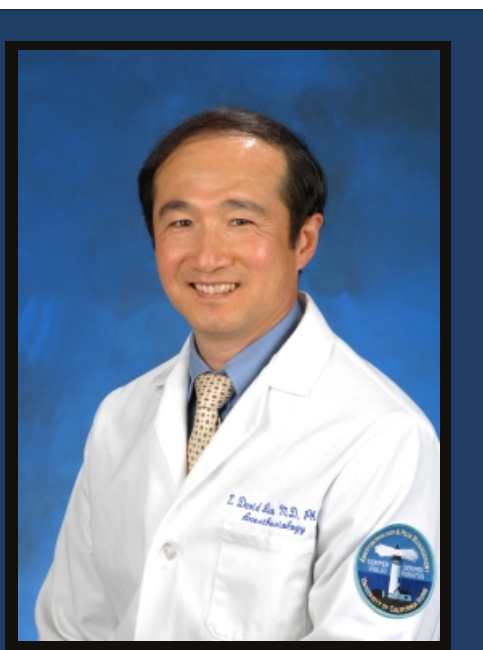
## RIRC WELCOMES Z. DAVID LUO, M.D., PH.D.

The Reeve-Irvine Research Center would like to welcome its newest member, Z. David Luo, M.D., Ph.D., a physician-scientist who is working on chronic pain mechanisms, including spinal cord injury-induced neuropathic pain. Actually, Dr. Luo is a "new" member of the RIRC in the sense that he has moved his lab from the UCI School of Medicine Campus in Orange to the Gillespie building, which houses the RIRC. Dr. Luo and Os Steward have been collaborating for several years on mechanisms of pain, and hold an NIH grant together. Being physically located in the Gillespie building will greatly enhance this and other collaborations.

Dr. Luo received his medical degree in China in 1984, then his Ph.D. degree in Biochemical Pharmacology from the State University of New York at Buffalo in 1993. After postdoctoral training in Molecular Pharmacology in the Department of Pharmacology at UCSD, including an Individual National Research Service Award from the National Institutes of Health (NIH), he was appointed an Adjunct Assistant Professor in the Department of

Anesthesiology, School of Medicine at UCSD. Dr. Luo relocated his laboratory from UCSD to UCI and joined the Department of Anesthesiology & Perioperative Care as an Assistant Professor in 2003. He was promoted to Associate Professor in 2009. Dr. Luo is also a joint faculty member in the Department of Pharmacology, and a member of the Chao Family Comprehensive Cancer Center at UCI.

Dr. Luo's research team utilizes three approaches to identify genes that are involved in the development and maintenance of abnormal sensations. First, they use gene chip analysis to assess changes in gene expression profiles in rodent models of chronic pain states. Second, they study how abnormal gene expression contributes to spinal sensitization, a central mechanism of abnormal sensations, using behavioral pharmacology, cellular and molecular biology, electrophysiology and immunohistochemistry techniques. Third, they use pharmacological agents, and molecular biology approaches to validate the causal roles of the gene pathways in chronic pain development. The overall goal of Dr. Luo's research is to identify novel factors or pathways that could be new drug targets for the development of more specific and safer pain medications.



**Dr. David Luo**

Dr. Luo's research accomplishments are well recognized in the pain research field. Dr. Luo has been invited to present his research findings in numerous international and national meetings and pharmaceutical companies, has established collaborations with investigators within UC Irvine and from other institutions around the world, has provided consultations to the private sector and various funding agencies in the United States and around the world, and has served on editorial boards and as associate editor for scientific journals related to pain and analgesia. Additionally, Dr. Luo has published two books in "Pain Research: Methods and Protocols," a cutting-edge collection of diverse readily reproducible techniques for dissecting the molecular mechanisms of pain. These methods employ a variety of multidisciplinary approaches ranging from experimental model systems to single neuron investigations.

Dr. Luo's research program has been supported continuously by extramural funding from NIH since 2000, the California Spinal Cord Injury Research Funds, private foundations including the Christopher and Dana Reeve Paralysis Foundation, as well as pharmaceutical company funding.

**Please join us in giving Dr. Luo and his laboratory a warm welcome to the Reeve-Irvine Research family!**

## Treatment of spinal cord injured rats with a combination of PTEN suppression and salmon fibrin shows potential for improvement of motor function recovery.

Gail Lewandowski, Ph.D.

### Why PTEN suppression and salmon fibrin?

As reported in previous newsletters, Os Steward's research group is collaborating with Dr. Zhigang He's research group at Harvard on approaches to enable corticospinal tract (CST) axon regeneration after spinal cord injury. One approach is to use a viral vector expressing small hairpin RNA molecules that selectively suppresses PTEN gene expression in rats (denoted AAV-shPTEN, see Spring 2012 Spinal Connections). When this gene therapy reagent (AAV-shPTEN) is injected into the brain, PTEN protein expression is suppressed by nearly 100% in CST neurons within the motor cortex. However, using this therapy to promote axon regeneration only solves part of the challenge for a successful spinal cord injury treatment. Another obstacle that needs to be addressed is the cystic cavity that forms in the chronically-injured spinal cord. This cavitation presents a barrier that prevents regenerating axons from connecting to spinal cord segments below the injury. Here, at the RIRC, we have been examining the use of salmon fibrin to treat the lesioned area (or cavity) of the injured spinal cord. While we do not know exactly how salmon fibrin works, Drs. Lisa Flanagan (Sue and Bill Gross Stem Cell Research Center) and Kelli Sharp (RIRC) found that salmon fibrin treatment in the spinal cord injury site promotes functional recovery (Sharp et al., 2012). Accordingly, we believe that the combined AAV-shPTEN and salmon fibrin treatment may provide a successful way to not only enhance axonal regeneration but encourage axonal regeneration through the lesioned site in the spinal cord.

### Will it work?

For the last year, Dr. Gail Lewandowski has been taking the next step to test whether the combination of AAV-shPTEN and salmon fibrin improves recovery of motor function after SCI. In a proof of concept study, Dr. Lewandowski used a skilled forepaw staircase-reaching task to test hand and arm function. In this task, rats reach for

food pellets placed on descending stairs. This task is a voluntary, skilled reaching task that requires arm, wrist, hand and digit dexterity. Thus, it is perfect for assessing motor function after cervical spinal cord injury. In the initial study, rats were trained in the skilled reaching task and then either AAV-shPTEN or a control vector (AAV-shLuc) was injected into the motor cortex of the brain. A few days later, all of the rats received a cervical spinal cord injury and then half of the rats were treated with salmon fibrin. Forelimb motor function was then tested for 10 weeks post-injury.

The results of this initial experiment are very encouraging and suggest that when AAV-shPTEN is combined with salmon fibrin treatment, there is a significant improvement in forepaw function recovery. Indeed, as early as 3 weeks post-injury, rats treated with the combination therapy were more successful at reaching the food pellets. Importantly, the forepaw function of these rats continued to improve during the entire course of the assessment period. In contrast, the forepaw function of rats in all the other treatment groups remained virtually unchanged during the 10 week assessment period. These results support the continued exploration of AAV-shPTEN and salmon fibrin treatment as a potential therapy for spinal cord injury.

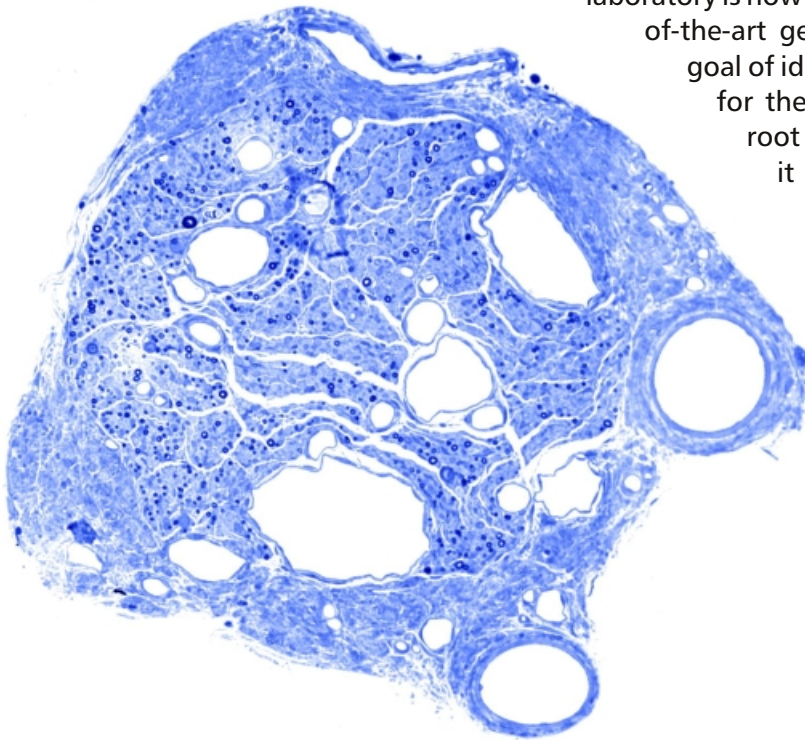
### What's next?

While the combination therapy appears to promote improved function recovery, how it works is still unknown. To address this, we are now assessing whether there is enhanced axon regeneration and cavity repair. This part of the analysis (the histological assessment) can take a number of months to complete. So, stay tuned for the next installment! The next critical next step will be to determine whether the treatment is effective if delivered in the chronic period after a spinal cord injury.

## Havton Laboratory Update

The Havton laboratory at the Reeve-Irvine Research Center studies spinal cord injury and repair with a special interest in developing new treatments for injury to the conus medullaris and cauda equina. These injuries affect the most caudal (or lowest) parts of the spinal cord and associated nerve roots and result in paralysis and bladder dysfunction. Earlier studies by the Havton laboratory have shown that it may be possible to surgically repair nerve roots that have been separated from the spinal cord by trauma. Specifically, he has shown in experimental models that the injured nerve roots may be re-attached to the spinal cord. This procedure enables regeneration of some axons from the spinal cord to peripheral targets, which can return some functions (reflex bladder function for example). Regeneration is limited, however, and the mechanisms behind this exciting improvement in function are not well understood. "We believe that the nerve roots, which are re-inserted into the spinal cord release several factors that stimulate growth of nerve fibers, but we do not yet know which factors contribute the most to the nerve regeneration in this setting", states Dr. Leif Havton.

Although the nerve fibers degenerate in the lesioned nerve roots, supportive cells within the roots are able to divide and are metabolically active. These supportive cells are believed to be responsible for the production of a variety of beneficial growth factors. Therefore, the Havton laboratory is now studying the injured nerve roots, using state-of-the-art genetic and molecular approaches, with the goal of identifying the factors that may be responsible for the nerve regeneration provided by the nerve root grafts. If the critical factors can be identified, it may be possible to develop ways to further promote regeneration.



Light microscopic image of an injured sacral nerve root, which normally carried motor and autonomic fibers. After injury, this root was separated from the spinal cord with loss of almost all detectable axons. However, the remaining supportive cells produce a variety of growth promoting substances that may stimulate nerve regeneration.

The team includes Dr. Arthi Amin and Dr. Harriet Chang in the Havton lab as well as Dr. Dan Geschwind and Dr. Giovanni Coppola at UCLA. "This collaboration brings together expertise in nerve regeneration and gene expression studies between two UC campuses and allows us to study thousands of genes simultaneously" explains Dr. Havton. His research team is hopeful that new treatment targets may be identified using this approach with the long-term goal being the development of new treatments in the future to overcome paralysis and restore bladder function after conus medullaris and cauda equina forms of spinal cord injury. Preliminary data from this project will be presented in November of 2013 in San Diego, CA, at the Annual Meeting for the Society of Neuroscience.



### *Research Medal, from the cover...*

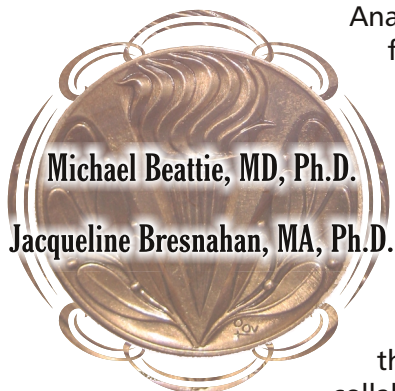
from 2000-2006. In 2006, Dr. Beattie and his wife and colleague Dr. Jacqueline Bresnahan, moved their laboratory to the University of California, San Francisco. He is now a Professor in the Department of Neurological Surgery and Director of Research at the Brain and Spinal Injury Center at UC San Francisco. His research interests include secondary spinal cord injury, cell death and repair, neuroinflammation, and recovery of function after CNS injury. Dr. Beattie has served on numerous NIH and foundation review panels, and is a member of the NIH CNNT study section, the Scientific Advisory Board of the C.H. Nielsen Foundation, and the editorial board of the Journal of Neurotrauma. He currently serves as the Vice-President of the National Neurotrauma Society.

Jacqueline C. Bresnahan received her BA in Psychology from Kent State University, and a MA and PhD in Physiological Psychology from Ohio State University, where she studied recovery of function after brain injuries. She completed her postdoctoral training in the Department of

Anatomy at Ohio State University, focusing on the anatomical consequences of spinal cord injury. She joined the faculty there in 1977, was promoted to Associate and then Full Professor in the Department of Neuroscience, and served as the Associate Dean for Basic Science from 2001 to 2006. She then moved with her husband and collaborator, Michael S. Beattie, Ph.D.,

to the Brain and Spinal Injury Center at University of California San Francisco, and is currently a Full Professor in the Department of Neurological Surgery. She has worked on spinal cord structure-function relationships, plasticity after injury, and especially, recovery of function after spinal cord injury. She has served on many NIH review panels, and was a member and chair of the NSD-A section. She served as a member of the Scientific Advisory Board for the Christopher Reeve Foundation and was chair from 2008-2012. She was an advisor for Acorda Therapeutics, and served on the editorial boards of the Journal of Neurotrauma, Restorative Neurology and Neuroscience, and the Journal of Neurodegeneration and Regeneration. She also served as a counselor and president of the National Neurotrauma Society and is currently the president-elect.

Together with their students and colleagues, they are currently focusing on bringing exciting findings from basic research to the clinic for application to human spinal cord and brain injuries. Congratulations Drs. Michael Beattie and Jacqueline Bresnahan.



## 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**

rirc@uci.edu  
949-824-3993

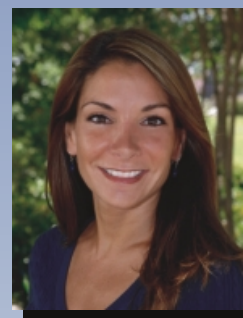


## Interested in fundraising or making a donation?

Please contact:

### **Tania Jope**

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



Spinal Connections  
is a publication of the

## Reeve-Irvine Research Center

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

As mentioned in one of the Anatomy 101 sections in our last newsletter (number 22), there has been a lot of buzz surrounding neural stem cells (NSC) in the spinal cord injury (SCI) field. In March 2011 the first NSC clinical trial, initiated by Stem Cells Inc and based on the work of Drs. Aileen Anderson and Brian Cummings, for SCI was approved by the FDA. In January of this year the second NSC based clinical trial for SCI was approved, this one initiated by NeuralStem Inc and based on the work of Drs. Mark Tuszynski and Paul Lu. In our previous newsletter we dissected what NSCs were and what they could do for SCI.

Here, we wanted to put together information and compare, in a friendly way, both of the currently approved NSC trials. Our intent is not to call attention to one over the other, as we are colleagues with both research parties involved,

# StemCells, Inc.

Sponsor	Responsible party		Information		Contact	
	<ul style="list-style-type: none"><li>Stem Cells Inc.</li></ul>		<ul style="list-style-type: none"><li>Clinical trial #: NCT01321333</li><li><a href="http://www.stemcellsinc.com">www.stemcellsinc.com</a></li></ul>		<ul style="list-style-type: none"><li>Armin Curt, MD Principle Investigator (PI) University Hospital Balgrist</li></ul>	
Study	Type / Phase of trial		Condition		Intervention	
	<ul style="list-style-type: none"><li>Interventional</li><li>Phase I/II</li></ul>		<ul style="list-style-type: none"><li>Thoracic spinal cord injury</li></ul>		<ul style="list-style-type: none"><li>Human CNS-stem cells (HuCNS-SC)</li><li>Single dose transplantation into spinal cord</li></ul>	
Enrollment	Status		Enrollment #		Est. completion date	
	<ul style="list-style-type: none"><li>Currently recruiting</li><li>Start: March 2011</li></ul>		<ul style="list-style-type: none"><li>12</li><li>Male or female 18-60 yrs old</li></ul>		<ul style="list-style-type: none"><li>Data completion: December 2015</li><li>Study completion: March 2016</li></ul>	
Eligibility	Inclusion criteria			Exclusion criteria		
	<ul style="list-style-type: none"><li>T2-T11 thoracic SCI based on ASIA level determined</li><li>T2-T11 thoracic SCI as assessed by MRI and/or CT</li><li>Must be at stable stage of medical recovery after</li><li>Minimum of 6 weeks post injury for initial screening</li><li>ASIA Impairment scale (AIS) grade at A, B, or C</li><li>Must have evidence of preserved conus function</li></ul>			<ul style="list-style-type: none"><li>History of traumatic brain injury without recovery</li><li>Penetrating SCI (stabbing or gun shot wound)</li><li>Evidence of spinal instability or persistent stenosis or compression due to initial trauma</li><li>Previous organ, tissue, bone marrow transplant, or any gene or cell transplant</li><li>Current or prior malignancy</li></ul>		
Outcomes	Primary outcomes			Secondary outcomes		
	<ul style="list-style-type: none"><li>Types and frequencies of adverse events and serious adverse events</li><li>One year after transplant</li></ul>			<ul style="list-style-type: none"><li>Not provided</li></ul>		
Description	<ul style="list-style-type: none"><li>This study will look at the safety of a single dose of HuCNS-SC transplanted into the thoracic spinal cord of patients with sub-acute spinal cord injury.</li><li>Subjects will all receive immunosuppression for the first 9 months after cell transplantation.</li><li>All subjects will also be enrolled in a long term, observational follow-up study (NGT01725880) for 4 years.</li></ul>					

no other details are provided by Clinical Trials.gov

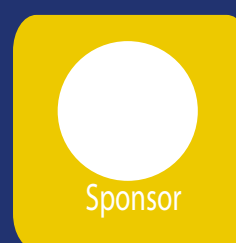


nor are we endorsing or promoting either of the NSC trials. Rather, we are simply describing each approved trial and some of the published pre-clinical work that helped get these trials off the ground. All of the information listed can be found on the ClinicalTrials.gov site (information from part I) or in published journal articles (information for part II to be covered in our next newsletter).

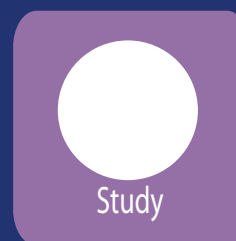
For part I of the "stem off", we have described the details of each clinical trial in the easy to ready comparison chart below.

*Please note that both of these trials are "neural stem cells", not human embryonic stem cells (HuESCs) as in the Geron trial. Any further medical questions or decisions related to these trials should be discussed with your physician.*

Responsible party	Information	Contact
<ul style="list-style-type: none"> <li>Neural Stem Inc.</li> </ul>	<ul style="list-style-type: none"> <li>Clinical trial #: NCT01772810</li> <li><a href="http://www.neuralstem.com">www.neuralstem.com</a></li> </ul>	<ul style="list-style-type: none"> <li>Neural Stem Inc.</li> </ul>



Type / Phase of trial	Condition	Intervention	Location
<ul style="list-style-type: none"> <li>Interventional</li> <li>Phase I</li> </ul>	<ul style="list-style-type: none"> <li>Spinal cord injury</li> </ul>	<ul style="list-style-type: none"> <li>Human spinal cord derived Neural Stem Cells (HSSC)</li> <li>6 injections around injury into spinal cord</li> </ul>	<ul style="list-style-type: none"> <li>United States</li> </ul>



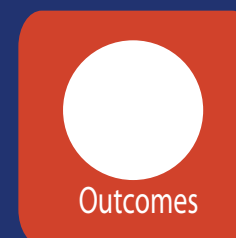
Status	Enrollment #	Est. completion date	Contact
<ul style="list-style-type: none"> <li>Not open yet for recruitment</li> <li>Start: April 2013</li> </ul>	<ul style="list-style-type: none"> <li>8</li> <li>Male or female 18-65 yrs old</li> </ul>	<ul style="list-style-type: none"> <li>Data completion: December 2013</li> <li>Study completion: February 2014</li> </ul>	<ul style="list-style-type: none"> <li>Keith Tansey MD, PhD</li> <li>404-603-4274</li> <li><a href="mailto:keith_tansey@shepard.org">keith_tansey@shepard.org</a></li> </ul>



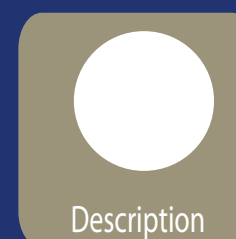
Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>T2-T12 thoracic SCI</li> <li>ASIA Impairment scale (AIS) grade at A det. by PI and a physical medicine and rehabilitation docotor</li> <li>Between 1-2 years after injury</li> <li>Confirmation of bone fusion by CT scan</li> <li>All vaccinations must be current at time of enrollment</li> </ul>	<ul style="list-style-type: none"> <li>SCI involving complete spinal cord transection</li> <li>Penetrating SCI (stabbing or gun shot wound)</li> <li>Eitology of paraplegia or weakness due to other neurological issues</li> <li>Receipt of any investigational drug or device (within 30 days) or other cell infusion</li> <li>Evidence of syrxin, cysts on the spinal cord or other medical concomitant diseases or conditions</li> </ul>



Primary outcomes	Secondary outcomes
<ul style="list-style-type: none"> <li>Measure the incidence of adverse events in patients</li> <li>Assessed over 60 month period</li> </ul>	<ul style="list-style-type: none"> <li>Evaluate the ability of HSSC to affect the AIS motor and sensory scores, bowel, bladder, pain, UAB IMR scores, SCIM scores and evoked sensory and motor potentials</li> </ul>



Description
<ul style="list-style-type: none"> <li>This study will determine the safety of HSSC transplantation for the treatment of chronic SCI.</li> <li>HSSC will be transplanted into 6 sites surrounding the injury: 2 at the rostral and caudal edges of the injury site and one segment length inferior to the injury site on each side of the injury site.</li> <li>4 patients will receive a total of 100,000 HSSC; 4 patients will recieve a total of 200,000 HSSC.</li> <li>All patients will receive immunosuppression with mix of Basiliximab, tacrolimus, and mycophenolate mofetil with a gradual withdraw at 13 weeks post transplant.</li> <li>All patients will ve followed at 2 weeks, monthly for 6 months and then every 6 months for 60 months.</li> </ul>



Neuralstem, Inc.

## Anatomy 101: The Bladder is Getting (phat)-ter

By Maya Hatch, PhD

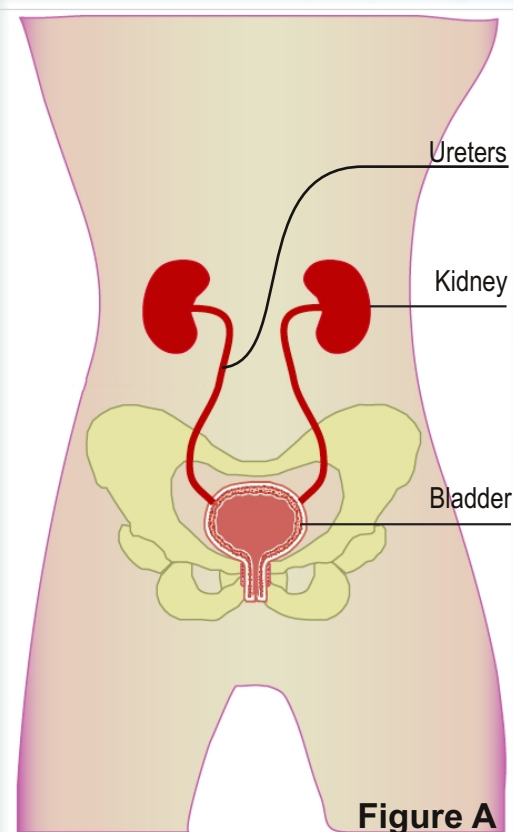
As many of you long time readers know, the Anatomy 101 section of our newsletter describes or explains various aspects of spinal cord injury (SCI) research or related topics and terms. We consider this section a mini tutorial on all things SCI and we often choose the topics based on other articles in the newsletter that need explaining or on hot topics in the SCI field and community. Since joining the RIRC, Dr. Leif Havton has written updates on his research, some of which involve bladder studies in SCI. However, besides a previous Anatomy 101 article by Dr. Suzy Kim (Spinal Connections 18) on the neurogenic bladder, we have not written much about the bladder and SCI. So finally, here are the basics of bladder control and SCI, with other topics to come.

### What's the phat-ter all about?

According to the online slang dictionary, Merriam-Webster online, and general street talk *phat* is a slang word that means 'new', 'cool' or 'highly attractive'. So why is the bladder getting phat-ter? Well, until recently bladder studies in the SCI field have been fairly limited. This is partially because we, as a field, have only started to understand the mechanisms involved in SCI-induced bladder dysfunction and control. It is also because the SCI research field has largely focused its efforts on locomotor recovery (or walking) and related functions. This however, has taken a turn recently. In 2004 Dr. Kim Anderson, while a member of the RIRC, published an eye opening article showing recovery of bladder and bowel function as the highest priority of individuals with SCI, even above walking. Additionally, recent statistics from Denmark show that approximately 54% of people with chronic SCI have some sort of chronic bladder or urological issue and this percentage is much higher when including those that have intermittent or temporary urological issues. These findings emphasize just how important bladder dysfunction is for the SCI community and how important it is to find interventions that can reduce or alleviate it. Indeed, more and more researchers have gotten involved in various aspects of bladder control after SCI, from basic research investigating the mechanisms and causes of bladder dysfunction to interventions that can help alleviate and improve bladder control. Several non-profit foundations, as well as companies, are also putting money into studies or interventions related to bladder management. In short, bladder-related studies and research are becoming more prevalent and a *phat* area of current SCI research.

### The urinary tract.

The bladder is an elastic bag-like sac located in the pelvis that stores urine (or liquid waste) produced by the kidneys until it is expelled from the body. It is made up of smooth muscles that expand and contract easily, and is capable of holding around 400-600 ml of urine (13 - 20oz). In an uninjured situation, the bladder is relaxed until urine produced by the kidneys is filtered into the bladder through a pair of thin tubes called ureters (see figure A). As urine enters, the bladder expands and, once filled to a certain point, two physiological responses are triggered that enable urination. One response is autonomic and called the micturition reflex. In the micturition reflex, sensory nerves transmit signals to the sacral region of the spinal cord (green line in figure B). Nerve cells (neurons) in the sacral region of the spinal cord transmit signals back to the muscles of the bladder wall (the detrusor) causing them to contract or squeeze (yellow line). The second response is that neurons in sacral region of the spinal cord also transmit signals to the brain, leading to the conscious desire to urinate. If urination is not desired (wrong time, wrong place), the brain sends signals back to the micturition reflex circuit (yellow line), inhibiting it. Impulses from the brain are also sent to the neurons that control the external urinary sphincter (blue line) to keep it contracted (and therefore closed), further preventing urination. The phrase "hold it?" describes the physiology perfectly.



When the person is ready to urinate voluntarily, the brain stops sending the inhibitory signals to the micturition reflex circuit in the spinal cord, releasing it from inhibition and simultaneously stops sending inhibitory signals to the spinal circuits that control the external urinary sphincter causing it to relax and open. The coordinated action of contracting the detrusor via the micturition reflex and relaxing the external urinary sphincter (called detrusor-sphincter synergy) expels urine.

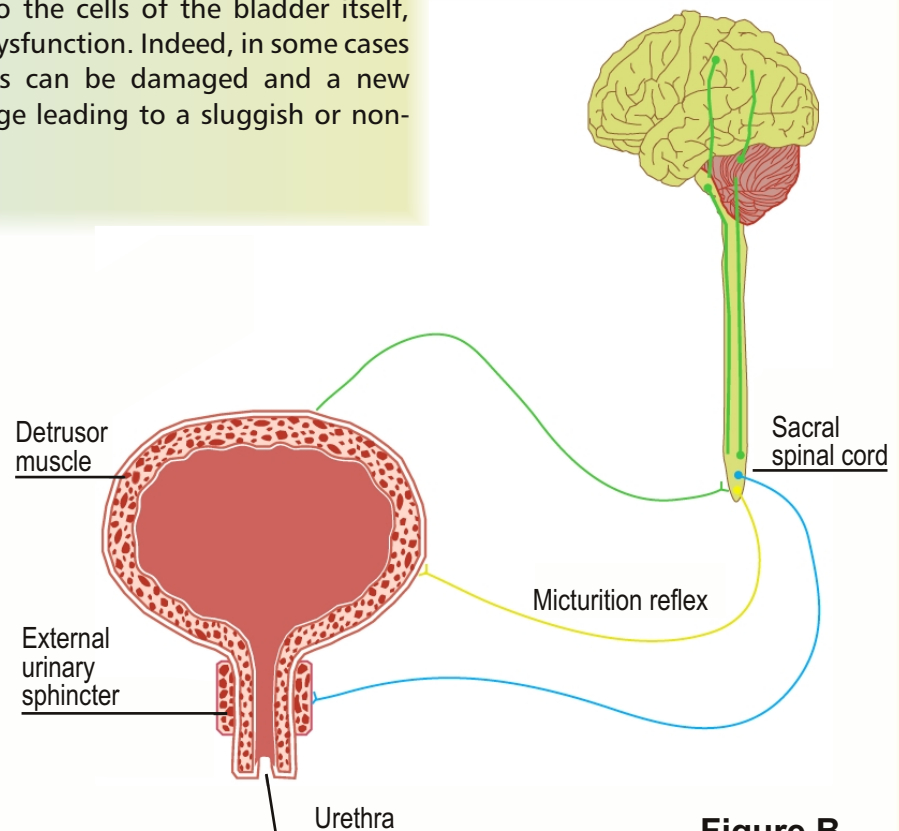
### Changes in the bladder and bladder pathways after SCI

The extent of bladder dysfunction from an SCI varies depending on the level, duration, and severity of the spinal cord injury. The primary effect of SCI is the interruption of signal transmission to and from areas below the injury to the brain, eliminating the ability to voluntarily control voiding. Injuries above the sacral level interrupt these pathways and injuries at the sacral level damage the micturition reflex circuit.

In most cases directly after injury there is a period of bladder areflexia (the failure of the bladder to respond to stimuli), causing urinary retention. At this stage, catheterization is important to prevent kidney damage and urinary tract infections (UTI's). Bladder areflexia can last from weeks to months. Eventually, as the spinal cord tries to recover and repair itself, a new micturition reflex can emerge. This can lead to the recovery of reflex bladder function, which occurs independently of brain signals, so that voiding is triggered automatically when the bladder is full. However, in most people, recovery of reflex bladder function is not sufficient because of detrusor-sphincter-dyssynergia (DSD). In DSD, the external urinary sphincter remains tightly closed at the same time that the detrusor contracts, leading to pathological increases in intra-bladder pressure. Therefore even though a new micturition reflex is established to help empty the bladder, DSD can still lead to urine retention. Ineffective or inefficient bladder emptying is of great concern as it causes the accumulation of large amounts of urine; and hence the bladder actually gets fatter (which is not "phat"). This inefficient bladder emptying can result in infections, damage to the upper urinary tract and, in some cases, can lead to autonomic dysreflexia (see Spinal Connections 13 for a description of AD).

In addition to DSD and AD, individuals may also have neurogenic detrusor overactivity (NDO), where the bladder is constantly contracted and leaking, or detrusor underactivity (NDU) where the detrusor fails to contract, which also leads to urine retention. There are also changes to the cells of the bladder itself, adding yet another level of bladder dysfunction. Indeed, in some cases the reflexes of the bladder muscles can be damaged and a new micturition reflex cannot even emerge leading to a sluggish or non-reflexive bladder.

As you can see there are many different forms and levels of bladder dysfunction in SCI individuals. Although our knowledge about the mechanisms leading to bladder dysfunction is improving, there is still a strong need for improved understanding of the electrical, organizational and neurochemical changes that occur in the brain as well as in the lower spinal segments of the spinal cord relative to bladder control. Now, with more and more researchers working on bladder-related studies we hope that we can find answers to help improve bladder control.



**Figure B**



## Profile...Dr. Camelia Danilov



This month, we're pleased to profile Dr. Camelia Danilov, who has been working as a Postdoctoral Researcher in Os Steward's lab since October 2011 on the CST/PTEN project described in previous newsletters.

Dr. Danilov received her Ph.D. from the University of Maryland in 2008 in Dr. Gary Fiskum's lab. Her dissertation assessed how oxygen levels influence the life and death of astrocytes in an in vitro model of the types of stroke that involve an interruption of blood flow, which deprives brain tissue of oxygen and glucose. Most stroke studies focus on neuronal death but astrocytes die too, and astrocytes are important for supporting neurons. Camelia found that high levels of O<sub>2</sub> during reperfusion (the time after the initial ischemic event when blood flow is returned to the brain) actually causes oxidative stress and exacerbates astrocyte death. She also found that Sulforaphane, a compound found in cruciferous vegetables, is neuroprotective and significantly reduced ischemia-induced astrocyte death by promoting antioxidative pathways.

Camelia then went on to do her first postdoctoral fellowship at the University of Washington, Seattle in Dr. Richard Morrison's Lab where she studied structures within cells called mitochondria. Mitochondria are the parts of the cell responsible for creating metabolic energy necessary for cell function. Recent evidence has shown that mitochondria are highly dynamic and essential for neuronal stability. Mitochondria change their size and shape by undergoing fission and fusion, processes which are important for mitochondrial regulation in neurons. During her time in Dr. Morrison's lab, Camelia studied how different isoforms of a mitochondrial fission protein, dynamin-related protein 1 (Drp1), regulate mitochondrial function and fission in neuronal and non-neuronal cells. The importance of this work is highlighted by the fact that several neurodegenerative diseases result from mutations in mitochondrial fission proteins.

Camelia left the tissue culture and mitochondrial world to broaden her research skills and dive into spinal cord injury research, specifically the CST/PTEN project described in previous newsletters. The original paper published in Nature Neuroscience in 2010 established that genetic deletion of PTEN enabled remarkable regeneration of the corticospinal tract (CST) after a spinal cord injury (SCI)<sup>1</sup>. The initial study involved genetic deletion of PTEN in newborn mice, which is easier to accomplish than in adult mice, but from a clinical standpoint, if PTEN is to be a viable therapy it has to be delivered after the injury not before. Showing that this is possible is an important milestone in bringing the PTEN story to potential clinical application. To this end Camelia's work examines the effect of PTEN deletion shortly after a SCI in adult animals.

Her experiments will not only assess CST regeneration, but will also test whether there is recovery of motor function, which was not done in the original paper. To this end, she is using the cervical contusion injury model developed in our lab and testing forelimb function, which is of very high priority for people who have suffered SCI at the cervical level. Thus Camelia's studies are also addressing a second critical milestone in the PTEN story—whether the regeneration that can be achieved is sufficient to reverse paralysis. Stay tuned for progress reports.

## Congratulations to our Recent RIRC Grad!



Chris Sontag with Dr. Aileen Anderson

## Steward Receives Norman M. Weinberger Award

The Reeve-Irvine Research Center congratulates Dr. Oswald Steward for receiving the 2012 Norman M. Weinberger Award. This award was established by UCI's Department of Neurobiology and Behavior in honor of Dr. Norman M. Weinberger and it recognizes a lifetime of distinction in research, teaching and service. The awards ceremony was held at UCI on Tuesday, April 9th in the Herkoltz Conference Room at the Center for the Neurobiology of Learning and Memory (CNLM) where Dr. Steward gave a presentation to faculty and students. Dr. Steward's presentation entitled "Protein synthesis at synapses, synaptic plasticity and memory consolidation; how chance favors the prepared mind" covered discoveries from his early days on polyribosome location in central nervous system (CNS) neurons to his current work on mRNA targeting to synapses. In addition to his scientific work Dr. Steward also shared stories, mnemonics and philosophies that Dr. Weinberger conveyed to him when Dr. Steward was a graduate student at UCI, making the presentation both informative and entertaining.



**Drs. Oswald Steward and Norman Weinberger**

Dr. Norman Weinberger was one of the original faculty members at UCI, one of the early Chairs of the Department of Neurobiology and Behavior and a founding fellow of the CNLM at UCI. Dr. Weinberger's laboratory is unique in that it combines two separate fields of neuroscience: auditory neuroscience and learning and memory. Currently his research team investigates the acquisition, retention and

**ResearchforCure** 

## 2013 Golf Tournament



**Saturday, October 5th**



**SOS Club in Modesto**

**819 Sunset Ave, Modesto, CA 95351**

**For more information on participating  
or sponsorship opportunities contact:  
Fran Lopes (209) 406-7812**

representation of information in the cerebral cortex that underlie behavioral memory. His recent work has shown how complex memories can be promoted by areas of the sensory cortex not previously known to be involved suggesting that the primary sensory cortex is a substrate of memory rather than just a sensory analyzer. In addition to his research on learning and memory, Dr. Weinberger served as an Associate Dean and Dean of the School of Biological Sciences, chaired numerous Academic Senate committees and received a number of outstanding awards within the scientific community. As the award suggests Dr. Weinberger is recognized as a superb teacher, and he continues to play a significant role in the progress of the CNLM. Now approaching his 50th year of research, Dr. Weinberger's laboratory is as active as ever and he is always willing to share his ideas, thoughts and experiences with colleagues. He is a true inspiration in neuroscience, and Dr. Steward is especially honored to receive this award.

## Unrestricted Giving: the fuel for progress

Six million people in the United States live with some form of paralysis, and approximately 1.3 million are paralyzed because of a spinal cord injury (SCI). Spinal cord injury profoundly alters one's life physically, mentally and financially. In addition to losing the ability to walk or use their hands, individuals also suffer other invisible impairments such as loss of bowel, bladder and sexual function, and in some cases, even loss of ability to breathe independently. Many people with spinal cord injuries also suffer from pain that is refractory to current drugs.

Until recently, spinal cord injury was considered to be un-treatable. Some doctors still deliver this horrible message. Today, however, our researchers are making discoveries that are changing this outlook. We urgently need funding to launch new studies and accelerate existing ones. Research at the RIRC focuses on SCI, but our studies could also lead to new therapies for traumatic brain injury and stroke and diseases such as Parkinson's Disease, Huntington's Disease, Alzheimer's Disease, and multiple sclerosis.

Additional funding accelerates discovery, but also allows flexibility to rapidly address new opportunities. Every dollar makes the research go further, and faster.

An unrestricted gift allows the RIRC to apply funds where they will have the most impact. For example your unrestricted gift might support:

- **Seed Money** - for new 'out of the box' research ideas, support for new projects that are spinoffs of existing projects to improve the quality of the potential treatment, as well as advancing projects that are underfunded.
- **Accelerating progress** - exciting new studies may have funding that is distributed over years but the studies could be done more quickly. You who are living with SCI want rapid progress and our researchers are ready and able to move research forward without delay to test potential therapies.
- **Equipment & Project support** - Any research project requires technical support; lab items must be ordered, finances must be tracked, animal research protocols must be prepared, and progress reports are required. Funds that are restricted to research cannot be used for these critical support services. Some equipment may be too costly for standard grant applications and/or may be restricted to one specific project. Unrestricted funds allow for cross use of equipment maximizing impact.
- **Public Events** - give an opportunity for those who suffer with an SCI injury to speak directly to our scientists to ask questions about their injury and to see first-hand the latest research that is being conducted through on-site tours.

These are just a few of the ways that unrestricted gifts/funds help us achieve scientific breakthroughs that help improving the lives of those who suffer this devastating injury and many related diseases and disorders.

### 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](mailto:tania.jope@uci.edu)



# New BCI System Creates a Buzz in the Technology Field

Brain Computer Interfaces (BCI's) are computer based systems that are able to decode specific brain signals and then use those signals to operate external devices (for more information on BCI technology and how it works, please see Spinal Connections number 21 "Are You Ready To Be a Cyborg"). These types of devices have the potential to dramatically change the quality of life for SCI individuals since they can completely bypass the areas of motor dysfunction or impairment. UC Irvine's Dr. Zoran Nenadic, an Associate Professor in the Department of Biomedical Engineering and Dr. An Do, a Clinical Instructor in the Department of Neurology at UCI and at the Long Beach Veterans Affairs Medical Center, have been working on a new BCI system that interfaces with a robotic gait orthosis to enable walking. The concept of this device was propelled by previous results from this group, supported by Roman Reed funds, where able-bodied and SCI subjects used an EEG BCI cap to control the walking of an avatar within a virtual reality environment, suggesting that accurate BCI control of ambulation was possible. The new BCI device (shown in the figure) uses the same EEG-based cap but, instead of controlling an avatar on a screen, it interfaces with leg braces attached to a treadmill. Once strapped in, test subjects were instructed to imagine walking or standing at various times. The BCI device matched the appropriate brain signals (optimized during training sessions) to the right action, which then automatically manipulated the robotic leg braces to start or stop walking accordingly.

The results from an able-bodied subject (<http://www.youtube.com/watch?v=W97Z8fEAQ7g>) have been presented at the IEEE workshop on Brain-Machine-Body Interfaces, and featured by WIRED SCIENCE and The Huffington Post. In their next step the team of collaborators, including engineers, physicians and physical therapists, recently received support from the National Science Foundation (NSF) to study the ability of this device to work on paraplegic subjects. This past summer, the system was successfully tested on its first SCI subject (<http://www.youtube.com/watch?v=HXNCwonhjG8&feature=youtu.be>) with additional subjects lined up. Although more testing needs to be done to further validate this device, and much more research on BCI technology in general needs to be performed, it is still a significant breakthrough in the technology field. Indeed, these results confirm the feasibility and enhance the practicality of BCI-controlled prosthesis for paralyzed individuals. Although we may not be ready for such technology to be common-place yet, it is definitely a step in the right direction.

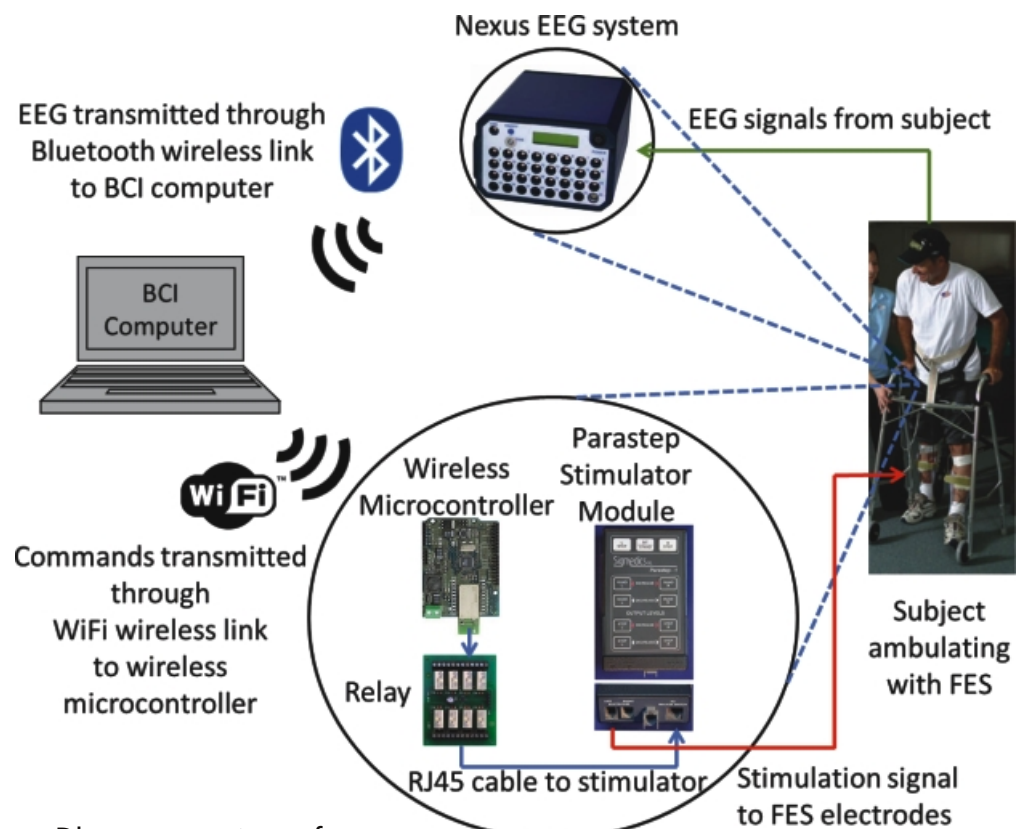


Diagram courtesy of  
Dr. Zoran Nenadic

Link for Huffington Post: [http://www.huffingtonpost.com/2012/09/06/mind-controlled-robotic-legs-paralyzed-walk\\_n\\_1862078.html](http://www.huffingtonpost.com/2012/09/06/mind-controlled-robotic-legs-paralyzed-walk_n_1862078.html)

Link for WIRED SCIENCE: <http://www.wired.com/wiredscience/2012/09/brain-controlled-robotic-legs/>

## *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](mailto: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](http://www.reeve.uci.edu)**

## **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](mailto:sci@uci.edu) or call (949) 824-5145

## **New at the RIRC!**

### **Monthly Lab Tours**



For more information  
on touring the laboratories  
and hearing more about our research programs  
please contact

Kelli Sharp, DPT  
[sci@uci.edu](mailto:sci@uci.edu) or call (949) 824-5145



## **Plymouth Rock N' Run**

**1K/5K/10K Run/Walk**

Yorba Regional Park

Nov 28, 2013

Thanksgiving  
Morning



**[www.plymouthrocknrun.com](http://www.plymouthrocknrun.com)**

Race registration:

<https://racewire.com/register.php?id=3255>