

Spinal Connections

He Made the World a Better Place: a Sad Goodbye to Robin Williams



He made us laugh, he was a humanitarian with a huge heart and he was Christopher Reeve's dear friend. The world lost a comedy legend and a beautiful man when Robin Williams passed away on August 11, 2014. Robin left a profound impression through his performances, the numerous charities he supported and with everyone he encountered.

Robin Williams was one of Christopher Reeve's dearest friends. After Christopher's devastating equestrian accident in 1995, Chris was initially very depressed. In Christopher's book "Still Me" he reflected on his wife Dana who stood by his side and told him that if he wished to pull the plug they would "find a way to do that" she added, "But you are still you and we love you." And it was at this point that Robin Williams entered the picture.

To give a little background to the story, readers may not know the links between RIRC and the University of Virginia (UVA) Hospital, where Christopher was initially treated. At the time of Chris's injury, Os Steward was the Chair of the Department of Neuroscience at UVA with a joint appointment in the Department of Neurosurgery. Dr. John Jane, Chair of the Department of Neurosurgery who was Chris's neurosurgeon, hired Os as a starting assistant professor years earlier. Tania was also at UVA, working for Os in the Department of Neuroscience. So we were there at the time when Chris was being treated. During the time that Chris was at UVA, the hospital was surrounded by news vans and reporters. Nevertheless, the medical team caring for Chris found a way to sneak Robin Williams past the assembled press dressed as a doctor. Robin entered Chris's room wearing a mask and posing as a proctologist planning to do an exam. This was the first time

Christopher laughed after his injury. In a later interview with Barbara Walters,



Robin Williams with Jessica Yant and Jessie Steward

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Dr. Oswald Steward

News reports of recovery after transplants of olfactory cells with peripheral nerve bridges

Many of you will have seen news stories reporting functional regeneration of connections that enable movement in a man that received transplants of olfactory cells. This approach is a clinical realization of decades of research by a scientist who received our Reeve-Irvine Research Medal in 2005 (Geoff Raisman). The findings are provocative, and the overall study reflects a huge effort by a skilled team of researchers and medical doctors. Unfortunately, though, the situation is not as simple as implied in most of the news stories. So, what is this all about, and what does it mean for those of you living with paralysis?

First the science: the overall approach builds upon years of research on regeneration of nerve connections from the nose to the brain. The ability to smell is mediated by nerve cells in the nose called olfactory receptors, which are embedded in a structure called the nasal mucosa, which is made up of receptor cells and mucosal cells. The olfactory receptors respond to chemicals in the air, and communicate via connections (axons) that project into the brain. The olfactory receptors in the nose "turn over" throughout life (that is, the cells die and others are born), which is different than almost any other part of the nervous system. When new cells are born, they have to grow their axons from the nasal mucosa in the nose into the olfactory bulbs, which are inside the skull. The olfactory bulb is connected to the brain by the olfactory nerve. To grow from the olfactory mucosa to the brain, the axons grow through the bony structure between the nose and the brain called the cribriform plate, and there is lots of evidence that growth is enabled by a special population of glial cells there called olfactory ensheathing cells (OECs). Dr. Raisman and other scientists have provided strong experimental evidence that OECs have special properties in terms of supporting axon growth, and many scientists have tried different ways of transplanting either OECs or the entire nasal mucosa into the injured spinal cord to promote regeneration.

Based on the studies in animals, quite a few people throughout the world have received a highly experimental therapy involving transplants of olfactory mucosa into the spinal cord. This experimental therapy is not available in the United States, but has been offered in Portugal and elsewhere, and some Americans have traveled to other countries to receive the transplants. These weren't clinical trials, however;

they were experimental therapies without controls or follow-up testing, so there's no scientific data on outcomes. Also, there are concerns about the approach of transplanting olfactory mucosa because of the recent finding of a tumor that developed in the spinal cord in a patient that received such a transplant (see our Spring 2014 newsletter).

It's important to emphasize that this new study involves cells that were isolated from the olfactory mucosa, not the olfactory mucosa itself, so the risk of tumor formation is hopefully less. Another good thing about this new study is that it was actually a clinical trial with an experimental and control group with extensive pre- and post-operative testing, so there is a lot of data. The patients were a total of 6 men between the ages of 22 and 26; 3 patients received the treatment, 3 did not, and all were tested extensively. The study reported outcomes 1 year after cell transplantation. The treatment in this new study, which was carried out in Warsaw Poland, was to transplant OECs that were harvested from the patient (autologous transplants) along with small pieces of peripheral nerves that were inserted to provide a bridge across the injury site. The first step was a complicated surgery to remove the olfactory mucosa.

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Transplants of olfactory cells continued

The olfactory mucosa was then dissociated (meaning broken up so that individual cells are in a mixture—imagine rice mixed with water) and the cells were transferred to a tissue culture dish for several days. The cells were characterized extensively while growing in culture, and at the end of the cell culture period contained OECs as well as other cell types. Then, each patient received another surgical procedure to open the spine and visualize the spinal cord so that the transplant could be done. Then, there was a lot of rehabilitation and testing.

Of the 3 people who received transplants, 2 exhibited improved function on the ASIA scale, the third did not improve on the ASIA scale, but did experience some improvement in sensation just below the injury. The main recovery in all patients was between 6 and 12 months post-transplant. For the man who was featured in the news reports who exhibited the greatest recovery, the first signs of recovery were 6 months following the treatment, and involved tingling sensations below the injury. By 8 months, the patient recovered some ability to feel touch below the injury. By 1 year, the patient had "...a slight voluntary flexion of the right hip" which qualified for conversion of the ASIA grade from A to C.

It's important to emphasize how the authors summarized the results: "... patients who underwent the operation of OEC transplantation combined with intense pre- and postoperative neurorehabilitation showed modest neurological signs of recovery." This highlights the fact that was a carefully done and carefully interpreted study with a lot of details, although even with that, some of the claims are provocative.

The title of the article claims "functional regeneration" (meaning growth of axons across the injury site). This claim was based largely on neurophysiological studies involving stimulation and recording of muscle responses (motor evoked potentials). This

"... patients who underwent the operation of OEC transplantation combined with intense pre- and postoperative neurorehabilitation showed modest neurological signs of recovery."

would be extraordinary if true. The authors were actually a lot more conservative in the paper itself, noting that even when injuries are functionally complete, there are usually some spared connections that could recover the ability to transmit. In fact, the authors conclude that the neurological recovery in transplanted patients may have been "...a combination of remyelination of spared demyelinated axons, stimulation of regeneration of lesioned axons towards the target host neurons, and reactivation or sprouting of surviving axons."

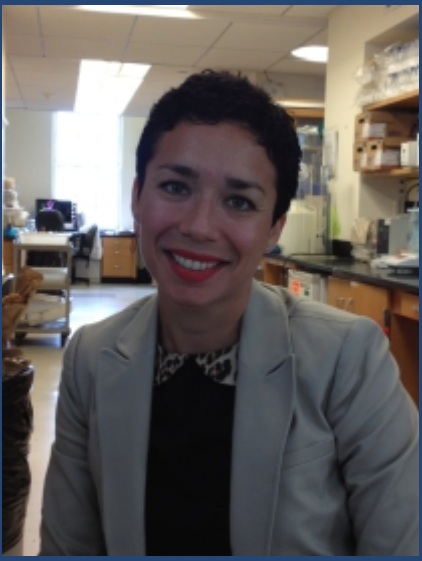
It's also important to note that the man who was featured in the news reports became paralyzed as a result of a stab injury, which caused extensive but incomplete laceration of the spinal cord leading to paralysis of the legs. This is a different situation than occurs with most spinal cord injuries that result from blunt force trauma like car accidents, diving injuries and falls, which cause contusion injuries. It is possible that the greater recovery in this patient is due to the type of injury.

So, the important thing is that this study was carefully done and produced a lot of scientific data that will form the basis for future studies. The surgical and cell culture procedures used here are complicated, and even in the best case, the neurological recovery was modest. The cost of the therapy would likely be several hundred thousand dollars per patient because of two surgical procedures, the lab work to grow the cells, and intense rehabilitation that extended for months. Only time will tell whether this could ever be adopted as a practical and effective therapy.

This was published in an open access journal, so you can download the original article (<http://www.ingentaconnect.com/search/article?option2=author&value2=tabakow&pageSize=10&index=1>)

Reference: Tabakow, P., G. Raisman, W. Fortuna, M. Czyz, J. Huber, D. Li, P. Szewczyk, S. Okurowski, R. Miedzybrodzki, B. Czapiaga, B. Salomon, A. Halon, Y. Li, J. Lipiec, A. Kulczyk and W. Jarmundowicz (2014). "Functional regeneration of supraspinal connections in a patient with transected spinal cord following transplantation of bulbar olfactory ensheathing cells with peripheral nerve bridging." *Cell Transplant*

The RIRC Welcomes Mariajose Metcalfe-Lilliewood



We're pleased to welcome Dr. Mariajose Metcalfe-Lilliewood as a new member of the RIRC Team. Her main responsibilities will be to manage and coordinate the spinal cord injury experiments in Dr. Oswald Steward's laboratory, but she will also be involved in training students, our public education programs, and coordinating collaborative research programs involving multiple investigators.

Mariajose comes to us from the Burke Medical Research Institute – Weill Medical College of Cornell University in White Plains, New York. Mariajose received her Bachelor of Science degree in Biological Sciences at Pontificia Universidad Católica de Chile in Santiago Chile. She completed a Masters of Science Degree and then completed her Ph.D. in Neuroscience in 2011 at The Graduate Center of City University of New York. Her dissertation research examined manipulations of cAMP as a potential therapeutic strategy against tauopathies, which are a family of human neurodegenerative disorders affecting the protein Tau. From 2011 until now, she has been a postdoctoral fellow with Dr. Brett Langley where she learned techniques of spinal cord injury research using rodent models. Her postdoctoral research tested compounds that might improve functional recovery in rodents after spinal cord injury (SCI) by (a) examining whether

inhibition of a microtubule-modifying enzyme, called HDAC6, promotes axon regeneration, and (b) whether increasing neuronal NAD⁺ levels (an intermediate in energy metabolism) limits neuronal degeneration.

Mariajose is a member of the New York Academy of Sciences, Society for Neuroscience and the Society of Biology Chile. She'll be arriving in California from New York with her husband James and Ethan her 16 month old son in early December.

"I'm really looking forward to joining the Reeve-Irvine Research Center. It is a tremendous honor to be part of an institution that is world-renowned and a leader in spinal cord injury research. When I visited the center I was impressed with the faculty, students, post-doctoral fellows and staff. With them and my background, I'm certain that we will work great together".

Please join us in welcoming Dr. Mariajose Metcalfe-Lilliewood to the Reeve-Irvine Research Center's team.

Robin Williams, continued from cover

Chris said, "I knew if I could laugh I could live". Christopher worked tirelessly for the rest of his life to increase awareness and increase funding for scientific research for spinal cord injury.

Today the Reeve-Irvine Research Center proudly wears his name and functions daily in honor of Christopher's mission to seek treatments that will eventually lead to cures for SCI. RIRC scientists have made important advances in developing stem cell therapies, developing ways promote regeneration of nerve connections, and developing other approaches to improve the lives of people living with SCI, including but not limited to, studies on pain, bowel and bladder function & brain signal connections through rehabilitation.

The support of his friend Robin helped to make this possible not only by being Christopher's friend; but by personally supporting his efforts to bring awareness and funding to SCI research. The bond that Robin and Christopher shared was special. Chris and Robin became friends before they enrolled in the prestigious Julliard School of Performing Arts in New York. As roommates in Julliard their friendship grew very close. Robin and Christopher made a promise to each other that they would support each other, and Robin continued to support Chris in many ways including attending fundraising events for the Christopher and Dana Reeve Foundation. We were fortunate to meet Robin at some of these, where he was as charming in person as he was on stage.

Dr. Maya Hatch moves to the Department of Veterans Affairs



Dr. Maya Hatch has been part of the Reeve-Irvine Research Center for many years. Many of you may be familiar with her research as a graduate student, articles that she has written for the Spinal Connections Newsletters or interacted with her through our public and educational events like

“Meet the Scientists” event. Now, Maya is taking the next step in her career development through a fellowship with the Department of Veterans Affairs (VA).

Maya was a graduate student with Dr. Hans Keirstead’s from 2005-2011. Through her experiences in her graduate degree, she became aware of the gaps between research in the lab, the clinical management of persons with SCI, and the accessibility of information to the community. After completing her Ph.D, Maya decided to focus on clinical research in SCI, specifically Comparative Effectiveness Research (CER). Comparative Effectiveness Research is a type of research that directly compares different health care interventions (tests, procedures, treatments) to treat, prevent or diagnose various health conditions.

Two years ago, Maya began the transition to CER through her appointment in the RIRC as Assistant Clinical Specialist and Education Coordinator. In this role Dr. Hatch conducted her own research, coordinated continued medical education symposia, enhanced our research collaborations with UCI physicians in other departments, and coordinated the funding through the Roman Reed Spinal Cord Injury Program until it was eliminated from the state budget. During her time at the RIRC, Maya also spearheaded (and is now running) a clinical trial sponsored by Aspen Medical Products on bracing for the treatment of chronic lower back pain.

With the experience gained at RIRC, Maya was awarded the fellowship at the VA, which will allow

her to spend full time on CER research. Co-mentors for the fellowship will be the director of the SCI/D division for the VA, and the co-director of the VA’s SCI/D Quality Enhancement Research Initiative (SCI-QUERI). Her research will focus on how the VA’s health information technology (specifically their personal health record portal), and patients access to it, impacts healthcare utilization and costs. This will be analyzed in regards to general conditions as well as to SCI patients specifically. Indeed, the VA has a long history of performing this type of research and they are one of the few organizations heavily invested in improving SCI care.

In addition to her fellowship at the VA, Maya will maintain involvement with the RIRC by continuing to work on various SCI research projects (especially those related to stem cell therapies or applications), foster collaborations with other physicians interested in SCI management/care, and hopefully bring future clinical trials or clinical studies to UCI and the RIRC.

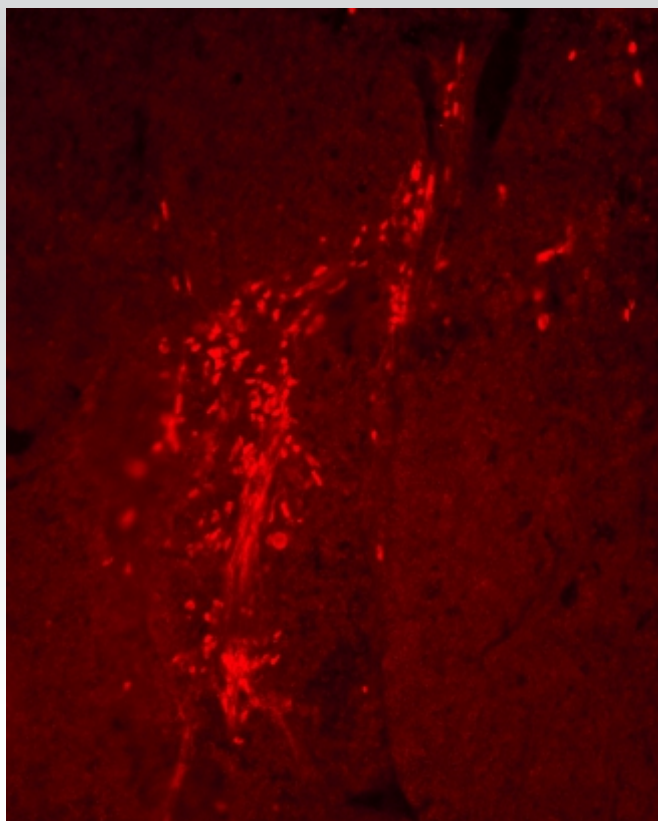
All of us at RIRC look forward to continuing to work with Maya in her new role.



Havton Laboratory Update

Using Stem Cells to Improve Bladder Function after a Low Spinal Cord Injury

Stem cells have the potential to become any cell of the body and after a spinal cord injury researchers have used them to replace everything from the supporting cells of the nervous system to the actual cells that transmit information from the brain to different parts of the body. The Havton lab at the Reeve-Irvine Research Center and the Sue & Bill Gross Stem Cell research Center at UC Irvine is utilizing stem cells to replace cells located in the low lumbar and sacral regions of the spinal cord that are injured after a trauma to the lumbosacral spinal cord and nerve roots. Physicians often refer to these injuries as conus medullaris or cauda equina injuries. After a low spinal cord injury the bladder may become underactive because spinal cord motor neurons that normally signal the bladder to contract are either dead or dying. As a result, the bladder tends to fill up more than it should, because the affected individual is unable to sense the fullness of the bladder or empty the bladder voluntarily. Such over-filling of the bladder can lead to urinary tract infections, kidney disease or overflow incontinence. Ongoing research in the Havton lab focuses on the nerve cells in the spinal cord that normally contract the bladder and cause voiding. For this purpose, stem cells are used in laboratory models to replace the injured and lost motor neurons. The goal of the study is for cell replacement therapy to improve bladder function and the quality of life of people living with a low spinal cord injury.



In collaboration with Drs. Harley Kornblum and Bennett Novitch at UCLA, the Havton lab has developed a method to convert stem cells into a mix of motor neurons and support cells in the dish and transplant the cells into the spinal cord of rats. Ongoing studies are using a cauda equina injury model and the cell transplantation strategies to determine feasibility of this approach to reverse functional deficits of the bladder. Special attention is paid to see whether the transplanted cells may survive over long periods of time after transplantation and reconnect with the peripheral targets in the pelvis to restore bladder function. The collaborative and translational studies have received support from California Institute of Regenerative Medicine (CIRM). Dr. Arthi Amin, a post-doctoral fellow in the Havton lab, will present results from this ongoing study in November at the annual meeting for the Society for Neuroscience in Washington, D.C.

Example of transplanted human stem cell derived motor neurons into a rat spinal cord in the attempt to improve bladder function after a conus medullaris or cauda equina injury.

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Congratulations Dr. Sharp

Everyone at RIRC is so excited about the accomplishments of Dr. Kelli Sharp, which have resulted in her being appointed as Assistant Professor in the Department of Dance at the University of California Irvine. Dr. Sharp's unique background in spinal cord injury research and her doctorate training in physical therapy evolved into a laboratory that focuses on the development of rehabilitation tools and protocols to improve the quality of life of individuals suffering from spinal cord injuries, traumatic brain injuries (TBI), and cerebral vascular accidents (CVA). Her research focuses on the development of novel technologies to advance rehabilitation strategies by incorporating tools, such as motion capture systems and functional magnetic resonance (fMRI) with dance/movement therapy. Over the long term, these new rehabilitation and assessment tools will be important for clinical trials of therapies to enhance motor and sensory recovery. We are thrilled that Dr. Sharp plans to continue her research in the iMOVE lab located in the Sue & Bill Gross Stem cell Research Center, that many of you have visited at our Meet the Scientists event!

Just to take you back, Kelli was one of the original members of the RIRC, coming to UCI with Os Steward from the University of Virginia in 1999. But the links go even further back. Kelli was a friend of the Steward family for a decade before coming to RIRC. Kelli was an equestrian and competed against (and with) Jessica Steward, Os's daughter starting when the two were in middle school (Os has pictures). For some of the time, they had the same trainer, and both went on to compete at the collegiate level on the equestrian teams of their respective colleges.

When Kelli graduated from college, she applied for a lab job at the University of Virginia, and the senior technician in Os's lab hired her (when Os was out of town). Kelli moved with Os from UVA to establish the RIRC, and has been an integral part of the RIRC team since its inception in 1999.

At RIRC, Kelli initially helped to establish and manage Dr. Oswald Steward's animal research. But she was interested in human research, so at the same time she was working full time in the RIRC, she earned a doctorate in Physical Therapy (DPT) from Chapman University in 2008. Her role then evolved from Lab direction and animal experiments to research on human subjects. After receiving her DPT, Dr. Sharp launched into an NIH funded research project with Drs Steve Cramer and Suzy Kim. The study involved testing of mental visualization and physical practice to determine if it can improve walking function in people with spinal cord injuries. The experiment also used functional magnetic imaging to determine brain function and was carried out at UCI and the University of Cincinnati. Subsequently, she's collaborated with Drs. Steve Cramer and David Reinkensmeyer on studies of ways to improve motor function after spinal cord injury and stroke, at the same time that she led animal studies in the RIRC.

Her appointment as an Assistant Professor in the Department of Dance brings a new dimension to Kelli's research. Dance is a highly skilled motor function, and training in dance is in many ways a model for re-training people to improve motor function after SCI and stroke. Her new position will provide new links that could lead to incredible new insights.

My experience at the RIRC helped to mold my career as a scientist and as an advocate for community outreach. The collaborations and everlasting support I have received from Dr. Steward, the members of RIRC, and the spinal cord injury community have been invaluable to me. The overwhelming support has provided me with the resources and intellectual experiences needed to take this next step in my academic journey. I plan to continue to work closely with the members of RIRC and the community to follow my passion of helping those with neurological disorders. In my new position in the Department of Dance, my research program embodies two pillars. The first pillar focuses on injury prevention and wellness for dancers using motion capture system and applying methods of analysis to determine the relationship of motion in space in order to reduce injuries. The second pillar focuses on the development of novel technologies to advance rehabilitation strategies for individuals with neurological disorders by incorporating tools, such as motion capture systems and functional magnetic resonance (fMRI) with dance/movement therapy. I will be conducting a study focusing on improvement of hand function after chronic SCI in the spring, so please stay tuned to future research endeavors. —Kelli Sharp

Please join us in congratulating Dr. Kelli Sharp, DPT. in her new position as Assistant Professor in the Department of Dance in the Claire Trevor School of the Arts at the University of California!



Dr. Kelli Sharp, Tom Pilgram & Dr. Steward

CHRONIC PAIN CHANGES YOUR BRAIN IN AREAS IMPORTANT FOR REWARD AND EMOTION

Anatomy 101 Cahill Lab Update

The most effective class of drugs available for treating moderate to severe pain is opioid drugs, such as morphine, hydrocodone (Vicodin®) and oxycodone. Opioids have been used (and abused) for centuries with uses ranging from religious rituals to treatment of dysentery, however, their prominent use in treating moderate to severe pain in modern medicine will undoubtedly continue for the foreseeable future, due to the lack of alternative choices. Most experts would agree that despite the fears of addiction and the plethora of side effects that may limit use, opioid drugs are superior analgesics for the treatment of post-operative pain, traumatic injury-related pain, and cancer pain. However, their long-term use in management in chronic non-malignant pain is now being challenged, where concerns about safety and efficacy are debated.

Over the past 2 decades there has been a tremendous effort by basic scientists, biotechnology companies and the pharmaceutical industry to develop new drugs to alleviate pain. Various drug candidates made it from preclinical testing to clinical trials, only to have failed and consequently many companies have now abandoned their pain programs. Those new drugs that have made it to market are primarily restricted to spinal delivery, limited to use in terminal cancer patients, or are based on success of drugs with similar chemical structure (e.g. pregabalin, which was developed after the success of off-label use of gabapentin which rose to over 1 billion annual sales in the USA). Some analysts blame the lack of drug development for pain drugs in the trial design and/or the patient cohort (type of pain patient recruited for the trial). However, there is also a debate about whether the preclinical testing can capture pain.

Pain is a multidimensional experience comprised of sensory, cognitive, and affective (emotional) components, which are processed within discrete but interacting brain structures. It is well accepted that many chronic pain states, including those that result from spinal cord injury, are accompanied by dramatic sensory disturbances that result in pain hypersensitivity (allodynia – painful experience to something normally not painful and hyperalgesia – exaggerated response to something normally painful) and tonic (unprovoked) ongoing pain. Preclinical animal pain model testing captures the sensory component by measuring the time to respond to a painful stimulus. However, the emotional affective component, or how much the pain is ‘bothersome’ or unpleasant significantly impacts the quality of life of the sufferer. Most animal models of chronic pain typically rely on sensory/threshold measures of pain, but the emotional component of pain has been argued to be a greater measure of quality of life than its sensory component, and there is now a concerted effort to develop assays to capture this aspect of pain with the goal of better predictability of drug candidates. Capturing this aspect of pain is a challenge because you can’t ask a mouse or rat how it feels.

Future directions - How do we proceed? There is fascinating new research indicating that the “bothersome” unpleasant component of chronic pain engages parts of the brain called the limbic system. Within the limbic system are brain regions important for being able to experience something we like (rewarding) or something we try to avoid (aversion). The key point is that pain and reward are opposite processes, but are processed within overlapping or interacting brain structures - see Figure 1. This is important because stimuli that are rewarding such as food and pleasurable music DECREASE pain, and conversely pain can impair reward processing (pleasure). So chronic pain can cause an “anhedonic state” in which a person can’t experience pleasure from activities usually found enjoyable (e.g., exercise, hobbies, music, sexual activities or social interactions). In fact, chronic pain is second only to bipolar disorder as the major cause of suicide among all medical illnesses, further highlighting how devastating this condition is. The interplay between reward pathways and pain validate the importance of these brain areas, not only in why acute pain becomes chronic, but also the minimal effectiveness of opioid analgesics in treating many types of chronic pain (including that of neuropathic origin).

On-going Studies: Dr. Cahill and her research team recently identified that there is dysfunction of reward circuitry in an animal model of neuropathic pain. So, pain changes reward circuits. Reward (pleasure) decreases pain perception, so disrupting reward circuits may increase pain because it

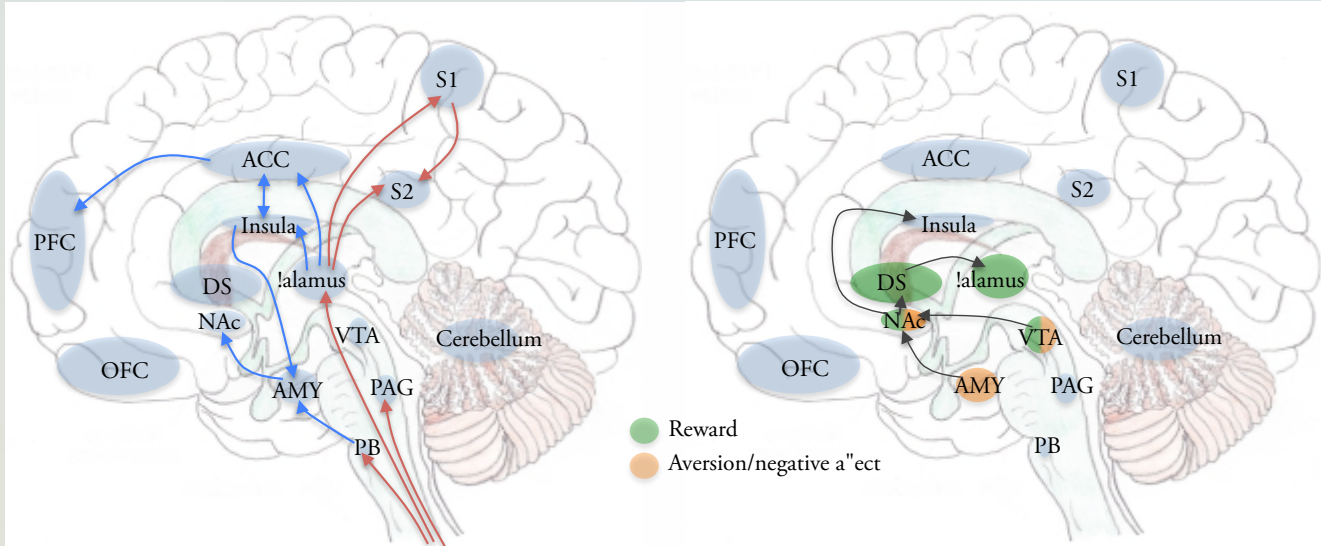


Figure 1. Cartoon of sagittal brain sections illustrating the networks involved in pain and reward/aversion.

Left: Network of sensory (red lines) and affective/cognitive (dashed blue lines) dimensions of pain. The sensory (red lines) pathway conveys information about location and intensity of pain. Neurons of the 'emotional' pathways (blue dashed lines) include brain regions important for fear, unpleasantness, subjective experience and autonomic and neuroendocrine stress responses. This circuitry is important for the subjective and emotional component of pain.

Right: Networks of circuitry involved in reward (green) and negative/aversion (orange). Note that many brain structures of the sensory and affective pain circuitry overlap with reward/aversion circuitry.

ACC (anterior cingulate cortex), AMY (amygdala), CC (corpus callosum), DS (dorsal striatum), HYP (hypothalamus), NAc (nucleus accumbens), OFC (orbitofrontal cortex), PAG (periaqueductal grey), PB (parabrachial nucleus), PFC (prefrontal cortex), S1 (primary somatosensory cortex), S2 (secondary somatosensory cortex), VTA (ventral tegmental area).

makes it more unpleasant. This is a major discovery, and the Cahill lab is now following up with research aimed at understanding the mechanisms responsible for the dysfunction of brain circuitry involved in emotion and reward in models of chronic pain. They are also preparing a proposal to seek pilot data for a clinical study aimed at novel therapies that will alleviate the emotional, affective component of pain.

This is early stage research—the follow up to a fundamental discovery, so additional data are needed before a clinical study can be launched. The Cahill lab is seeking federal funding, but this is where private contributions could make a HUGE difference, allowing these scientists to collect the critical preliminary data that would allow a clinical study of novel therapies to address chronic pain.

Congratulations!

Dr. Michelle Wedemeyer and Dr. Os Steward at her graduation. Dr. Wedemeyer is currently in her neurosurgery residency at USC.

**The Reeve-Irvine Center
Meet the Scientists Forum
Coming in the Spring, 2015
Check our Website for Updates
reeve.uci.edu**



Another Clinical Trial of Stem Cells for SCI is Launched.

In early October, the company Neuralstem Inc. announced that the first patient had been treated in their new Phase I clinical trial involving "Neural Stem Cells" (NSCs). In this trial, four patients with chronic thoracic level injuries (1-2 years post injury) will receive NSC transplants into the injury site. This trial is under the direction of Dr. Joseph Ciacchi, MD, UC San Diego School of Medicine and neurosurgeon at UC San Diego Health System. Much of the pre-clinical work with the NSI-566 cells in spinal cord injury was conducted at UC San Diego School of Medicine by Martin Marsala, MD, professor in the Department of Anesthesiology.

As described in our previous newsletters (see Spinal Connections #22, winter 2012), NSCs are stem cells that are already specified to a neural lineage. They are able to multiply and differentiate into all of the cell types of the nervous system including neurons, astrocytes, and oligodendrocytes. The goal of the treatment being tested in this trial is to inject NSCs into the injury site, where it is hoped that they will develop into a tissue bridge that will allow axons to grow across the injury.

The goal here is a bit different from other ongoing trials of stem cells for spinal cord injury. For example, in the Asterias trial, which continues the one started by Geron, the rationale was to use oligodendrocyte precursor cells (OPCs) derived from embryonic stem cells, which are injected near the site of injury in the hope that they will restore myelin and/or provide growth factors to help repair. In the ongoing trial by Stem Cells Inc., their proprietary NSCs are injected near the injury in the hope that they will develop into nerve cells and glial cells and/or provide growth factors to promote repair.

Neuralstem's proprietary NSC line is the one that was used for the ongoing ALS trial, in which 30 patients received transplants. This was primarily a safety trial, and no adverse events have been reported so far. A follow-up trial with larger numbers of patients to test efficacy for ALS is being planned.

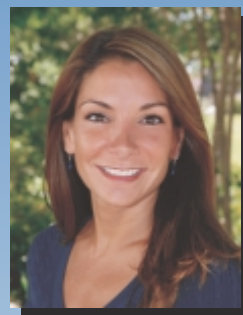
One cautionary note: Dr. Steward has also been studying NSCs as a means of bridging lesion sites. One surprising discovery this year involves NSCs that were treated with high concentrations of growth factors to promote their survival and expansion. In an experiment in rats, Dr. Steward discovered that about half the rats developed ectopic colonies of cells at long distances from the transplant. For example, following transplants into lesion sites at the thoracic level, colonies of stem cells were found in the cervical spinal cord and the brain. This work was first published in the journal "Cell" in early 2014 and a follow-up article was published in the Journal of Neuroscience in early fall. Dr. Steward is carrying out further studies to determine whether these colonies are harmful or not.

Reeve-Irvine Research Center

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

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Fundraising



**5k/10k Turkey Trot
Yorba Regional Park
27 November 2014**

Brought to you by **ResearchforCure**



The Plymouth Rock N Run's Turkey Trot is hosted annually on Thanksgiving morning at Yorba Regional Park in Anaheim Hills. Now in its 7th year, PRNR was established as a fundraiser to provide much-needed support for spinal cord injury research at the Reeve-Irvine Research Center (RIRC) at UC Irvine. Staffed

entirely by volunteers, PRNR's management team is an eclectic mix of working and retired professionals, athletic coaches, and runners whose passion and common goal is to put on a top-notch, family-friendly running event to benefit both the local community and RIRC via ResearchforCure*.

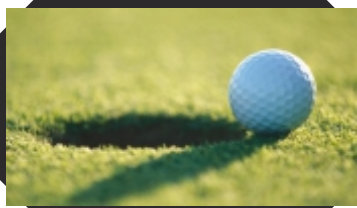
Since our inaugural run in 2008, PRNR has evolved from a small, grass-roots affair into an established Thanksgiving Day tradition, drawing many hundreds of participants from the North Orange County area and outlying communities. With each passing year, PRNR continues to grow in both prestige and popularity; To enhance this year's success we incorporated on-line crowd fundraising in an effort to increase gifts to the Center. The top team raised over \$3,000 in a few short weeks. Please consider becoming a fundraising team when you register for next year's race! With just a few emails to friends and family and a facebook posting your team can help magnify the overall proceeds from this event. The top fundraising team will be awarded a prize and of course, bragging rights.

PRNR's success is due in large measure to community support – in particular, to their sponsors who so generously donate goods, services, and funds to the event and its cause. Please consider being a part of the PRNR's growing family. There are several ways you can be involved, As an event sponsor and/or exhibitor at our vendor fair, Plymouth Rock 'n' Run is a rare opportunity for you to increase your exposure within the community, promote your products and services to thousands in this prime demographic area, and help make a real difference in the lives of those afflicted by spinal cord injuries and other neurological disorders.

The day is filled with prizes, costumes, and fitness for the whole family. There is a 1K kids race too! Please join us for the festivities and consider making a gift or being a sponsor if you can't attend. Every little bit helps!



ResearchforCure



The Reeve-Irvine Research Center would like to say a special thanks to the Research for Cure team for holding their Annual Golf Tournament in Modesto, California!

If you are interested in sponsoring this event or would like to join us next year please contact Tania Jope at tania.jope@uci.edu (949) 824-5925

Seasons Greetings

The holiday season reminds us of how grateful we are for your support of important research efforts being conducted at the Reeve-Irvine Research Center. Your kindness helps to provide hope to millions.

- ★ with the knowledge that your contribution will be used to advance research that is targeted to new treatments for spinal cord injury.
- ★ with the knowledge that for the first time in human history, there is legitimate optimism that neurological damage can be controlled and repaired.
- ★ recognizing that new treatments that relieve symptoms associated with spinal cord injury will be accompanied by economic advantages for individuals, their families, the state and the nation.
- ★ knowing that your gift will produce a visible difference.

Please consider making your year-end tax deductible gift now.

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** at (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 this address, or online at **reeve.uci.edu**

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



University of California, Irvine



Need something fun to do on Monday nights and support a great cause?
Join us for BINGO every Monday for the month of January!

At Chapter One Gastropub!
227 N Broadway, Santa Ana, CA 92701
Every Monday in January find us in the "Red Room".

Bingo is \$10 for 5 rounds (cash only please)

-We'll play 5 Rounds where guests can win "gag" gifts after each round. A 6th and final bonus round blackout will then be played, with a grand prize!

Proceeds Benefit the Reeve-Irvine Research Center at the University of California Irvine



Culinary, Craft Cocktails

Classic Dishes With A Twist

Social Dining At Its Finest