New breakthrough on regenerating connections after spinal cord injury

In last winter’s newsletter (#16) we announced the launch of a new collaboration between Dr. Os Steward’s research group and that of Dr. Zhigang He at Children’s Hospital, Harvard. The goal of the “Corticospinal Tract Regeneration Project” is to develop ways to promote regeneration of the connections that control our ability to move voluntarily. Damage to these connections following spinal cord injury is the cause of paralysis, and even a small amount of regeneration of this pathway could have a huge functional benefit for people who are paralyzed as a result of spinal cord injury.

In September, our team published their first major paper in the journal Nature Neuroscience*, which is one of the top tier journals in the field. We even got the cover photograph. In brief, the paper showed that deletion of a gene called PTEN enabled axons of the corticospinal tract to regenerate through a complete spinal cord injury. Nothing like this has ever been seen before. The paper has been called "A major advance in promoting recovery after spinal cord injury"; see Neurology Today, September 2010, by Richard Robinson.

So why is this considered a major advance? The reason is that it has never before been possible to induce regeneration of CST axons through a spinal cord lesion. There are actually two parts to this. 1) CST axons are considered to be highly refractory to regenerative growth in comparison to some other types of connections; and 2) the axons actually regenerate through a lesion, which is a huge barrier. The images tell the tale.

Imagine there’s Regeneration…. Deleting PTEN induces dramatic regeneration of CST axons through a complete crush injury in mice. If this could be achieved in people, it could restore motor function. The panel on the left is an MRI of a person with an injury at the cervical level. In this individual, the CST would be interrupted, and regeneration would not occur. The middle image (control) illustrates a comparable injury in mice. CST axons are labeled in red, and end above the lesion. The left panel shows the dramatic regeneration in a mouse in which PTEN is deleted in the cortex. Regenerating axons extend through the lesion into caudal segments.
Approval granted for a stem cell trial for chronic spinal cord injury based on research by Aileen Anderson and Brian Cummings

In a major step forward, approval has been granted by the Swiss equivalent of the Federal Drug Administration (FDA) of the United States, to launch a Phase I/II clinical trial that will transplant human neural stem cells into patients with relatively chronic spinal cord injuries (3-12 months post-injury). This trial will be run in Switzerland by the US company Stem Cells Inc., and is based on research by Aileen Anderson and Brian Cummings, members of the RIRC and now members of the Sue and Bill Gross Stem Cell Center. Their results reveal that human neural stem cells injected into the injured spinal cord differentiate into neurons and oligodendrocytes. Improvement in walking function was seen when cells were injected 1 month post-injury in mice, which is considered to be a relatively chronic injury in mice. Obviously, a treatment that could be used in people with chronic spinal cord injuries would be a huge step forward.

This will be a safety trial, but will also assess efficacy using defined clinical endpoints (so is a Phase I/II trial). According to press releases from Stem Cells Inc., the trial will enroll 12 patients with thoracic spinal cord injury, including those with both complete and incomplete injuries, classified as American Spinal Injury Association (ASIA) A, B, or C. Patient enrollment is expected to start during early 2011 starting with people with complete injuries (ASIA A) and then moving to cohorts with less severe injuries (ASIA B and C). Enrollment will be open to patients in Europe with thoracic spinal cord injury (injury level of T2-T11). Cells will be transplanted into the spinal cord, and patients will receive immunosuppression to prevent transplant rejection. Participants will be tested over a 12-month period to assess safety and evaluate any recovery of neurological function.

Neural stem cells are different from embryonic stem cells in that they were derived originally from brain tissue from an aborted fetus. Because they come from brain, the stem cells are restricted to a neural lineage, and will only differentiate (develop into) the 3 types of cells found in the brain and spinal cord—neurons, astrocytes, and oligodendrocytes. For this reason, they may be less risky in that they are unlikely to develop into tumors, which is a risk for embryonic stem cells.

Of note, approval for this trial was granted very quickly. The application was filed in October 2010, and approval was announced on December 7. The trial will be run in a way that is very similar to what would occur in the United States.

Congratulations to Aileen and Brian for this huge accomplishment!

Update on Clinical Trials based on research by RIRC scientists

**Geron trial is underway:**
This October, the first patient received injections of human embryonic stem cells that have been pushed to become oligodendrocyte precursor cells (OPCs). This Phase I trial is based on the work of Hans Keirstead and is being run by Geron Corp. In this trial, people who suffer injuries at the thoracic level (ASIA A complete) will receive injections of OPCs within 14 days after the injury. Seven medical centers throughout the United States have been identified as potential sites for the trial. The first patient received the OPCs in a surgical procedure carried out at Shepherd Center in Atlanta, Georgia.

**Application filed for a stem cell trial for spinal muscular atrophy based on research by Hans Keirstead:**
Also this October, California Stem Cell Inc. applied to the federal Food & Drug Administration to start a Phase I safety study on a stem cell-derived motor neuron transplantation treatment for spinal muscular atrophy (SMA). SMA is the leading genetic cause of death in infants, affecting motor neurons in the spinal cord and causing the deterioration of muscles that control crawling, walking, swallowing and breathing. This Phase I trial would test the safety of these cells when injected into the spinal cord of children suffering from SMA.

Filing the application to conduct a trial is not the same as getting approval. It could take months or even years (as in the case of the Geron trial) before the trials can be launched. Nevertheless, filing the application is a major step forward.
So, what’s next? To move this forward as a potential therapy, we have to answer 3 questions. The first is to find out whether the regeneration improves motor function. The experiments for the Nature Neuroscience paper focused on regeneration of connections and were not designed to answer questions about function. The experimental injuries were at mid-thoracic levels, and the regenerating axons grew for only a few segments—not far enough to reach the lumbar levels that control the hind legs. So now, we’re changing the experiments to assess regeneration after injuries at the cervical level, which causes loss of motor function in upper extremities in mice. Then, we test the same sorts of motor abilities that would be important for people with cervical spinal cord injuries, for example the ability to use the hands for gripping and manipulation. It’s complicated though because we have to do this in a way that doesn’t completely paralyze the mice, so lesions have to be incomplete.

The second step is to find out whether the treatment can be given after a spinal cord injury. In the experiments so far, we’ve deleted the PTEN gene before the spinal cord injury. We think it is likely to work after the injury too, but we need to show this directly.

The third and most important step for translation is to find a way to block PTEN function that can be used in people. We are working on two approaches, one involving drugs that block PTEN action, and the other using viral vectors that carry an “anti-gene”.

Our sincere thanks to Bob Yant who has been working hard to raise private funds to move this project forward, and for the enabling donation of Brad Wentz and Family, who provided funding for the CST regeneration/PTEN project in its infancy through the "Z" Fund, named in honor of Zach Wentz who suffered a spinal cord injury in early 2009. For more information on the PTEN project, contact Os Steward or Tania Cusack.

The Reeve-Irvine Research Center would like to welcome its newest addition, Leif A. Havton, M.D., Ph.D., a physician-scientist, who is working in the research fields of spinal cord injury and repair, pain, and stem cell science.

For this purpose, the laboratory performs behavioral and physiological studies, gene expression analyses, detailed anatomical investigations, including immunohistochemistry, neuronal reconstructions, intracellular neuronal labeling, and electron microscopy. Therapeutic interventions under current study in the laboratory include a variety of surgical nerve root repair strategies, pharmacological approaches, and transplantation of stem cell derived motor and autonomic neurons. The Havton laboratory has collaborations with multiple laboratories across the country and abroad.

Dr. Havton received his M.D. from Umea University School of Medicine, Umea, Sweden, in 1988, and his Ph.D. in Anatomy from the Department of Anatomy, Umea University School of Medicine, Umea, Sweden, in 1989. Dr. Havton’s Ph.D. thesis work was on the retrograde effects of peripheral nerve injury on intramedullary reflex pathways in the cat spinal cord. The work included a combination of single cell electrophysiology and tracer injections as well as detailed morphological reconstructions and electron microscopy.

Following his graduate studies, Dr. Havton immigrated to the United States and joined UCSF as a postdoctoral fellow in the Department of Anatomy for the period of 1989-1991. At UCSF, Dr. Havton studied the somatosensory thalamus in the rat, cat, and non-human primate using a combination of single cell electrophysiology and three-dimensional reconstructions of single cells. The studies were relevant for our understanding of sensory processing, including pain.

Dr. Havton continued his clinical training as an intern in medicine at the St. Mary’s Medical Center in San Francisco during 1991-1992. He continued his clinical training as a resident in neurology at Stanford University Medical Center during 1992-1995 and served as Administrative Chief Resident during 1994-1995. Dr. Havton received additional fellowship training in Pathology/Neuropathology at Stanford University Medical Center during 1995-1997. He also served as an attending neurologist at Santa Clara Valley Medical Center in San Jose (1995-2000) and as a Clinical Assistant Professor in the Department of Neurology and Neurological Sciences at Stanford University Medical Center (1998-2000). In July 2000, Dr. Havton joined the Department of Neurology at UCLA as an Assistant Professor and has since developed a new research in spinal cord injury and repair. At UCLA, he also served as an attending neurologist on the Neurologic Rehabilitation and Research Unit, providing care for patients with neurological impairments in both inpatient and outpatient settings. In July, Dr. Havton was promoted to Professor in the Department of Neurology, UCLA. Dr. Havton is board certified in Neurology (1995-2015).

The Havton laboratory currently receives research funding from the National Institutes of Health (NIH), the Department of Defense (DoD), the Veterans Administration (VA), the California Institute for Regenerative Medicine (CIRM), and the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation.
Dr. Gail Lewandowski is a Project Scientist in the Reeve-Irvine Research Center, at the University of California, Irvine. She has been at UCI since 2005 and has worked with Dr. Os Steward for the past 4 years.

Dr. Lewandowski hails from a dairy farm in central Minnesota and received her bachelor’s degree in biology from the University of Minnesota, St. Paul. She conducted her graduate research in the Department of Pharmacology at the University of North Carolina, Chapel Hill. As a postdoctoral fellow, she studied neuropathology with Dr. Floyd E. Bloom at The Scripps Research Institute in La Jolla, CA. Upon completion of her postdoctoral training, Dr. Lewandowski remained at TSRI as an Assistant Member investigating the impact of neural-immune molecules on neuronal function. Since that time Dr. Lewandowski has held positions in Biotechnology (Rockville, MD) and academia (UA, Tucson, AZ, and UNM, Albuquerque, NM). She has cultivated an extensive background in basic biomedical research. Her research expertise includes neuropathogenesis, molecular neurobiology, bioinformatics, and learning and memory.

Most recently in collaboration with Dr. Os Steward, Dr. Lewandowski has been working on a viral vector approach to enhance axon regeneration after spinal cord injury. Her project involves treating rats with a viral vector that expresses a molecule that inhibits a gene called PTEN. In adults, PTEN is involved with the cellular process that restrains axon extension. The hope is that the viral vector therapy will inhibit PTEN expression and allow injured axons to extend and regenerate. In another project, Dr. Lewandowski is studying the neuronal activity that occurs in the brains of rats during simple forepaw movement. Preliminarily, she has found that specific areas of the cortex that are activated while rats are performing forepaw movements may still have the potential to be activated after cervical spinal cord injury. Although, much more work needs to be done, these results may indicate the importance of mental practice and cortical stimulation after spinal cord injury.

Dr. Lewandowski will continue to bring her unique multidisciplinary conceptual and technical background to all of her studies in the RIRC and to the field of spinal cord injury research.

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Saturday March 12, 2011

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Professor and Attending Surgeon of Orthopedics and Neurosurgery
Thomas Jefferson University Hospital of the Rothman Institute,
Philadelphia, Pennsylvania

Meet the Scientists in March, date TBA
Centered around Dr. Vacarro’s visit
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www.reeve.uci.edu
Brian Cummings and Aileen Anderson receive CIRM grant for human neural stem cells to treat traumatic brain injury

In the latest round of grant funding, the California Institute for Regenerative Medicine (CIRM) funded “Early Translation Awards” that are designed to move good ideas out of the lab and into the clinic. The funded projects are expected to result in either a candidate drug or cell therapy or make significant strides toward such a candidate, which can then be developed for submission to the FDA for clinical trial. Brian Cummings and Aileen Anderson received one of these grants for their project to use human neural stem cells to treat traumatic brain injury. The grant will provide about $1.7 million over 3 years.

Traumatic brain injury (TBI) affects 1.4 million Americans a year; 175,000 in California. TBI is a common consequence of automobile accidents, and is a major cause of disability for our servicemen who suffer blast injuries. When the brain is injured, nerve cells near the site of injury die due to the initial trauma and interruption of blood flow. Secondary damage occurs as neighboring tissue is injured by the inflammatory response to the initial injury, leading to a larger area of damage. TBI damages both neurons, the electrically active cells, and oligodendrocytes, the cell that makes the myelin insulation. A TBI patient typically loses cognitive function in one or more domains associated with the damage (e.g. attention deficits with frontal damage, or learning and memory deficits associated with temporal lobe/hippocampal damage); post-traumatic seizures are also common. Currently, no treatments have been shown to be beneficial in alleviating the cognitive problems following even a mild TBI.

Drs. Cummings and Anderson have been working for some time with neural stem cells (NSCs), which are precursors of the 3 cell types in the nervous system. The idea is that transplanting NSCs into an injury would allow “cell replacement therapy”, in which the stem cells would differentiate into new neurons and new oligodendrocytes and fill in for lost host cells. An important part of the work is to sort the cells based on their intrinsic properties, which is accomplished using Fluorescence Activated Cell Sorting (FACS). They have successfully used "sorted" human NSCs in rodent models of spinal cord injury, showing that hNSCs migrate, proliferate, differentiate into oligodendrocytes and neurons, integrate with the host, and restore locomotor function. NSCs may also improve outcome by helping the host tissue repair itself, or by providing trophic support for newly born neurons following injury.

Recently, transplantation of rodent-derived NSCs into a model of TBI showed limited, but significant improvements in some outcome measures. These results argue for the need to develop human-derived NSCs that can be used for TBI. Drs. Cummings and Anderson will establish and characterize multiple "sorted" and "non-sorted" human NSC lines, determine their neural potential in cell culture, and use the best 2 lines in an animal model of TBI. They will determine whether transplants of NSCs improve cognitive function and reduce seizures following TBI. Ultimately, the goal is to generate one or more human NSC lines suitable to use for TBI and/or other CNS injuries or disorders. A small reduction in the size of the injury or restoration of just some nerve fibers to their targets beyond the injury could have significant implications for a patient’s quality of life.
One step further in restoring motor function after cervical spinal cord injury using stem cells

When you lift your arm, signals travel from your brain through motor neurons originating in the spinal cord, and further along their long projections to muscle fibers, ultimately resulting in muscle contraction. Loss of motor neurons is a characteristic feature of cervical spinal cord injury (SCI), causing a disconnection between the brain and the muscles that leads to a permanent loss of movement. A possible means to restore this function is to replace the lost cells with new motor neuronal progenitors, the precursors of motor neurons. All progenitor cells secrete survival-promoting (trophic) signals known to alter injury and disease pathogenesis, and thus serve as a potential source of support to the environment into which they are placed. However, no cell is an island, hMNPs from human embryonic stem cells (hESCs), and elegantly demonstrated anatomical and functional benefits exerted by the transplanted cells on the surrounding pathogenic environment in animal models of SCI. These results raise hope for a future therapeutic strategy within this field.

A primary requirement when replacing lost cells is to verify that the new cells consist of a pure cell population that is identical to the cells originally residing within the tissue. Thus, Rossi and her team initially demonstrated that hMNPs can be successfully generated from hESCs, and provided evidence that the cells expressed known markers for motor neurons, produced proper electrical signals required for muscle stimulation in living animals, secreted cellular growth- and survival-promoting factors, and showed the ability to functionally innervate human or rodent muscle in culture. In other words, they successfully generated cells that were molecularly and physiologically indistinguishable from naturally occurring motor neurons.

Having verified the equivalency between the hESC-derived hMNPs and motor neurons, the team brought the studies to the next level, where they investigated the survival and continued development of these cells in the injured adult rat spinal cord. In order to study this reciprocal interaction, they transplanted the high purity population of hMNPs into cervical spinal cord injured sites in adult rats. Shortly after the transplantation, the researchers observed significant improvements in the animals. They detected a suppression of signals associated with SCI pathogenesis, accompanied by increased survival and growth of cells already present in the spinal cord. These findings correlated with significantly improved functional performance of the rats. All together, these results indicate that the transplanted cells were able to change the internal environment of the spinal cord from a pathogenic to a growth supportive one, and restore the functional ability of the animals. However, the team also observed that hMNPs transplanted in close proximity to the injury site reverted to a less specified cell type, indicating that SCI still generates an environment that impedes neuronal maturation.

These remarkable results demonstrate the feasibility of using hMNPs to treat disorders characterized by loss of these cells. It is the first study to demonstrate anatomical and functional benefit following transplantation of a high-purity hMNP population to adult SCI, showing that the inherent trophic activity of transplanted hMNPs is sufficient to induce recovery in the pathogenic environment characterized by SCI. These findings suggest that this approach may be developed as a treatment for cervical spinal cord injury. The next step is to mature transplanted hMNPs and enhance their projections to target muscles in order to maximize the benefits of this cell population.
Embryonic stem cell therapy improves walking ability in rats with neck injuries. 
UCI study supports expansion of first human trial to include cervical spinal cord damage.

In an article published this year in the journal, Stem Cells, the laboratory of RIRC scientist Hans Keirstead reported that the first FDA-approved human embryonic stem cell-based treatment has been shown to restore limb function in pre-clinical studies of rats with spinal cord injuries in the region of the neck. In January 2009, the U.S. Food and Drug Administration gave Geron Corp. of Menlo Park, California, permission to test the treatment discovered at the Reeve-Irvine Research Center in people with thoracic spinal cord injuries, which occur in the spine at the level of the rib cage. However, it wasn’t approved for cervical injuries because pre-clinical tests on rodents had not been completed.

The treatment utilizes stem cells directed to become progenitors of spinal cord cells called oligodendrocytes. Oligodendrocytes form myelin, the biological insulation for nerve fibers, or axons, that is critical for maintaining electrical conduction in the central nervous system. Replacement of myelin by transplanted cells can potentially spare axons when myelin is stripped away through injury or disease, as in spinal cord injury. These cells can also support the injured cells in the vicinity of the trauma by expressing factors important for cell survival and function. In this study, rats were given the stem cell-derived treatment seven days after suffering a cervical spinal cord injury. Treated rats showed an increased range of motion compared to untreated rats. This increased mobility correlated with sparing of the neurons that innervate muscle, called motor neurons. Keirstead, graduate student Jason Sharp, and colleagues found the treatment not only prevented tissue death, it also trigger an increase in anti-inflammatory molecules, an effect not previously reported for these cells. “The transplant created a healing environment in the spinal cord,” said Keirstead.

Since the publication of this article, Geron Corp. has announced the first human embryonic stem cell-based treatment of a person with thoracic spinal cord injury. With the results of this study, Keirstead hopes the FDA will eventually approve the therapy for clinical testing to include people with cervical spinal cord injuries. About 52 percent of spinal cord injuries are cervical, and 48 percent are thoracic. “People with cervical injuries often have lost or impaired arm or leg movement, bowel, bladder or sexual function, and currently there’s no effective treatment. It’s a challenging existence,” said Keirstead. “What our treatment did to injured rodents is impressive. If we see even a fraction of that benefit in humans, it will be nothing short of a home run.”

In addition to Keirstead and Sharp, Jennifer Frame, Monica Siegenthaler and Gabriel Nistor of UCI worked on the study, supported by Geron Corp., a University of California Discovery Grant, the Roman Reed Spinal Cord Injury Research Fund of California, Research for Cure, and individual donations to the Reeve-Irvine Research Center.
In the latest round of grant funding, the California Institute for Regenerative Medicine (CIRM) funded “Early Translation Awards” that are designed to move good ideas out of the lab and into the clinic. The funded projects are expected to either result in a candidate drug or cell therapy or make significant strides toward such a candidate, which can then be developed for submission to the FDA for clinical trial. Our newest faculty member, Dr. Leif Havton, received one of these grants for his project to use human embryonic stem cells (hESCs) to derive motoneurons for spinal cord injury repair. The grant will provide about $1.6 million over 3 years.

Dr. Havton’s project focuses on injuries to the anatomically lowest part of the spinal cord, the lumbosacral portion and its associated nerve roots (called the cauda equina which is Latin for “horse’s tail”). Such injuries cause paralysis of the legs, loss of sensation, severe pain, as well as loss of bladder, bowel, and sexual function. About 20% of all spinal cord injuries are at the lumbosacral level.

As a result of the direct injury to the lumbosacral portion of the spinal cord, there is degeneration and death of spinal cord nerve cells (motoneurons) that control muscles in the legs as well as bladder, bowel, and sexual function. No treatments are presently available in clinical practice to reverse the effects of these devastating injuries. In order to reverse the loss of function after lumbosacral spinal cord injury, replacement of lost nerve cells is required. Dr. Havton’s project will develop a cell replacement therapy in which human embryonic stem cells are differentiated into the types of motoneurons that control both muscle and bladder function. The research program will test whether transplants of hESC-derived motoneurons can restore function in a clinically relevant rat model of lumbosacral spinal cord injuries. One very important part of the project is the plan to determine whether it is possible to deliver hESC-derived motoneurons in chronic injury settings.

Dr. Havton’s focus on bladder function is of unique importance. As a neurologist, he is acutely aware of the problems associated with the loss of bladder function in people with SCI. Indeed, as we all know from Kim Anderson’s survey several years ago, recovery of bladder function is one of the highest priorities for people who are living with SCI. It is no wonder because bladder infections are one of the most frequent causes of rehospitalization and disability for people with SCI. All of us on the RIRC team are excited that Leif has joined us, and that he will be addressing this important concern using stem cell approaches.

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**Leif Havton receives CIRM grant for Human Embryonic Stem Cell-derived motor neurons for spinal cord injury**

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“Spinal interneuronal networks: development, organization, plasticity, and targeting for rehabilitation of motor functions”

Over forty years ago, Joan Irvine-Smith, a well known Californian and philanthropist, played a lead role in the establishment of what is now the University of California at Irvine. Following Christopher Reeve’s tragic injury, and in recognition of his amazing spirit, she 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 grew to become the world-class research facility that it is today.

In 1996, the Reeve-Irvine Research Center and Joan Irvine-Smith established an annual award for research in spinal cord injury. The award, originally called the “Christopher Reeve Research Medal”, with Christopher’s blessing became the “Reeve-Irvine Research Medal” in 2003.

The Reeve-Irvine Research Medal recognizes an individual, or individuals, who have made highly meritorious scientific contributions in the area of spinal cord repair, and whose research has stood the test of time and scrutiny. The medal includes a $50,000 cash award generously provided by Joan Irvine-Smith and the Athalie R. Clarke 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 2008, nineteen exceptional researchers have received this prestigious award.

This year’s symposium was held at the Doubletree Suites Doheny Beach, Dana Point, California and had approximately 100 esteemed researchers in attendance. The Reeve-Irvine Research Center would like to congratulate the 2009 Reeve-Irvine Research Medal Recipients.

Marion Murray
Professor, Department of Neurobiology and Anatomy, Drexel University College of Medicine
Philadelphia, Pennsylvania

Elzbieta Jankowska
Professor Emeritus at the Department of Neuroscience and Physiology, University of Göteborg
Göteborg, Sweden

[Photo of Joan Irvine-Smith, Marion Murray, Elzbieta Jankowska, and Oswald Steward]
Elżbieta Jankowska, Ph.D.
Professor Emeritus, Department of Neuroscience and Physiology
University of Göteborg
Göteborg, Sweden

Dr. Jankowska is a highly respected expert in spinal cord physiology, especially organization of interneural circuitry in the spinal cord. Her research has elucidated the role of interneurons in spinal reflex pathways and in integrating the commands from descending motor pathways including the corticospinal, rubrospinal and reticulospinal systems. Her studies have shed tremendous light on how spinal circuitry actually works to control the coordinated activity of muscles. Taken together, the information points the way toward new therapeutic strategies for improving function after spinal cord injury.

Dr. Jankowska received her early scientific training at the University of Warsaw and obtained her Ph.D. degree at Nencki Institute of Experimental Biology also in Warsaw, Poland. She continued postgraduate studies at the Institut Marey in Paris, the Faculte de Medicine in Toulouse (France) and in the Dept. of Physiology, University of Göteborg (Sweden).

Dr. Jankowska has spent most of her professional career at the University of Göteborg where she held the position of research fellow (Swedish Medical Research Council), reader and professor before her retirement. Over the course of her career, she has also been a visiting scientist at the University of Toulouse and Centre National de Recherche Scientifique in Marseille (France), The Rockefeller University (NY, USA), University of Winnipeg (Canada), Australian National University (Canberra), Tsukuba University and National Institute for Physiological Sciences in Okazaki (Japan) and in Centro de Investigacion y Estudios Avanzados del Instituto Politécnico Nacional (Mexico City). Her work has been supported by research grants from the Swedish Medical Research Council and the National Institutes of Health (NIH) of the United States, the latest of which is funded through 2013. Funding by the NIH is a high honor, because projects outside the United States are funded by the NIH only under exceptional circumstances. She has published 202 original research papers and review articles, and her work continues to be highly cited in the field.

Dr. Jankowska has received many honors and awards including the Copernicus Medal from the Polish Academy of Sciences in 1993, the Doctor Honoris Causa from the Poznan Medical School in 1994, and was elected as a member of the Royal Society of Arts and Sciences in Göteborg. She has also been honored by invitations to present the Macallum Lecture at the University of Toronto (1981), the Servier Lecture at the University of Montreal (1995), and the Journal of Physiology Symposium on Spinal Cord Mechanisms and Rehabilitation dedicated to her during Neuroscience Meeting in New Orleans 2000.

Marion Murray, Ph.D.
Professor, Department of Neurobiology and Anatomy
Co-Director, Spinal Cord Center
Drexel University College of Medicine
Philadelphia, Pennsylvania

The focus of Dr. Murray’s career has been on neuroplasticity and its relation to recovery of function after CNS injury. The goal is to identify translatable therapies that can improve the lives of individuals with spinal cord injury. She has used a variety of animal models, including goldfish, rodents, and cats, to study the role of axonal regeneration and sprouting, neuroprotection, and activity in restoration of function lost through injury. Anatomical studies have shown that collateral sprouting occurs spontaneously in response to injury and that both sprouting and regeneration can be elicited by therapeutic cellular transplants. Neuroprotective strategies can rescue vulnerable neurons and promote sprouting of spared pathways. Pharmacotherapy can increase function of partially denervated circuits through actions on receptors upregulated as a result of loss of pathways and can diminish the inhibitory environment of the injured spinal cord. Training and exercise improves function through their effects on muscle, spinal cord and cortical pathways. Combinations of these treatments by acting through different mechanisms can offer further improvements.

Dr. Murray received a B.Sc (Hons) in Zoology from McGill University, an MA in Physiology from Harvard University, and a Ph.D. in Physiology from University of Wisconsin. Her postdoctoral work was done at McGill University in Anatomy and at the Rockefeller University in Neurobiology. She was appointed Assistant Professor in the Department of Anatomy at the University of Chicago and then moved to the Medical College of Pennsylvania (now the Drexel University College of Medicine). In Philadelphia, she and her colleague Michael Goldberger, set out to forge an interactive group of colleagues and collaborators focused on mechanisms of recovery of function following spinal injury. This group has been funded continuously by an NIH Program Project Grant since 1988. Drexel University College of Medicine created a Spinal Cord Research Center in recognition of their success. The group has also provided training in basic neuroscience for clinicians (neurosurgeons, neurologists, neuroradiologists, orthopedic surgeons, pathologists, physiatrists, urologists) who in turn have provided clinical insight into neurologic problems associated with SCI.

In 2005, Dr. Murray was appointed the Scientific Director of the Craig H. Neilson Foundation. This Foundation provides funding for the search for treatments for spinal cord injury and recovery of function at the basic, preclinical and clinical levels. This significant resource provides both an opportunity and a challenge to bridge the gap between the laboratory and the clinic and to make a difference in the lives of individuals with spinal cord injury.
Anatomy 101 - Hello, Neurogenic Bladder!
--Suzy Kim, M.D.

Do you often think about emptying your bladder multiple times per day? Staying continent? Locating the nearest bathroom? Does your bladder own you?

If you answered “yes” to any of the questions above, you are amongst the millions of people living with a neurogenic bladder. In fact, when an internet survey asked individuals with spinal cord injury (SCI) to rate what functional gain would improve their quality of life, bladder function ranked higher than walking amongst both paraplegics and tetraplegics. So, let’s get right down to it. Losing control of the bladder was rated the top concern for SCI individuals considering a sexual encounter.

If you have suffered any damage to your central nervous system, you may have problems with urinary leakage and bladder emptying. Where and to what extent the damage to the nervous system will help define the type of neurogenic bladder and the recommended ways to treat it. If you have a traumatic brain injury, stroke, spinal cord injury, multiple sclerosis or diabetes, you may need a daily catheterization program to empty your bladder. A simple pleasure of using the bathroom may not have been a preoccupation in the past, and the process of “potty training” as toddlers really underscores a complicated neurologic process. So, let’s go back to the basics of how we acquired urinary continence and the social confidence to drink that Venti Starbucks coffee.

Normal Bladder Function
There are 3 areas of the central nervous system that control the ongoing communication between the bladder and the brain: (1) cerebral micturition center, (2) pontine micturition center, and (3) sacral micturition center. The bladder has 2 main functions: storage and emptying of urine. Continence is then achieved if there is coordination of all three centers by the central nervous system.

As your kidneys continuously filter urine, the bladder functions to store and empty when the time is appropriate. Just like you don’t have to think about your heart beating or lungs breathing, normal bladder function also involves the autonomic nervous system - a part of the central nervous system that “automatically” controls our vital organs.

While the bladder stretches during the filling period, messages through peripheral nerves are communicated to the sacral micturition center and brain via the spinal cord. The brain (cerebral micturition center) then determines when it’s time to empty the bladder by communicating with the brainstem (pontine micturition center) to coordinate the contraction of the detrusor muscle that wraps around the bladder and the relaxation of the outlet sphincters located in our pelvic muscles via the sacral micturition center.

continued on page 13
Functional Classification of Neurogenic Bladder

Now, let’s talk about when this system goes awry. *Quick recap: the bladder functions to store and empty urine. If the main problem is storage, this will lead to urinary incontinence, which is defined as involuntary urinary leakage. Alternatively, if the main problem is difficulty in voluntary bladder emptying, this leads to urinary retention.*

Depending on the type and extent of injury to the nervous system, you may have a neurogenic bladder resulting in urinary incontinence, retention, or both. There are 3 types of neurogenic bladders: (1) spastic or hyperreflexic bladder, (2) flaccid or areflexic bladder, and (3) mixed bladder. An evaluation with a urologist and a variety of tests and procedures can determine the type and condition of a neurogenic bladder. These tests may include ultrasounds, CT scans and cystoscopy to evaluate the anatomy and urodynamics to determine bladder function. Generally, urologic evaluations are recommended annually or more frequently if you are having problems.

Bladder Programs

The goals of the optimal bladder program are to minimize medical complications such as urinary tract infections and damage to the kidneys; avoid bladder distention with adequate emptying of urine; and most importantly, choose the best option that fits your lifestyle and functional ability. Based on what type of neurogenic bladder you have, there may be several recommended bladder programs for you.

Among the methods to manage a neurogenic bladder, let’s highlight a preferred method called intermittent catheterization (IC). This is a method where a catheter is inserted into the bladder for drainage then removed several times per day. IC offers a means to empty the bladder without leaving a catheter in the bladder and wearing a urinary collection device, commonly a leg-bag. Studies have shown this type of bladder program minimizes the frequency of long-term medical complications such as hydronephrosis, autonomic dysreflexia, bladder and kidney stones, and urinary tract infections (UTIs). IC can be done by means of a clean or sterile technique. Clean intermittent catheterization (CIC) begins with hand washing and using a new or cleaned catheter. Sterile intermittent catheterization (SIC) uses a catheter in a closed bag or kit that protects the user from touching the inserted portion of the catheter (touchless catheter). IC is an optimal program for individuals who have adequate hand function to catheterize themselves, good compliance to adhere to a timed schedule, normal urethral anatomy and interest to not wear a collection device.

With normal bladder capacity of 500 ml, catheterizing the bladder every 4–6 hours prevents over distending the bladder but offers the potential for friction-related trauma to the urethra. With this frequency, a person will insert and remove a catheter 1500 to 2000 times per year! So, lubrication sounds like an obvious good idea right? Advanced technology now offers the use of many types of catheters. A traditional straight catheter will need lubrication prior to insertion, but has been found to not provide consistent lubrication through the urethra. Alternatively, a hydrophilic catheter may minimize the friction during insertion and removal due to its special coating as it passes through the urethra. Hydrophilic catheters are great options for men with enlarged prostate, those with difficulty in passing traditional lubricated catheters, and those with frequent UTIs or urethral irritation.

As there are medical, social and financial considerations in managing a neurogenic bladder, it is important to talk to your doctor to determine what method and bladder program is best for you.

Now, it’s time for you to own your bladder.

"This article can also be found on AstraTech’s website www.lofric.us, Bladdernews Issue # 12."

Resources:

www.pva.org “Bladder Management Following SCI: What You Should Know” and “Urinary Dysfunction and MS”
This year marks the third consecutive year for the annual Plymouth Rock N Run (PRNR) 5K and new 10k. PRNR, originated by student and jazz musician, Tim Johnson, started out as a small grass roots event. Over time the Plymouth Rock N Run group has evolved into a huge community event that is executed entirely by volunteers from the local community. Much of the support has come from students and staff of the Canyon and Esperanza high schools, including a number of talented performers who provide live musical entertainment along the route on race day. This year’s race, held at the Yorba Regional Park drew close to 1400 runners and continues to grow in tradition and popularity.

The Plymouth Rock N’ Run annual 5K/10k fun-run facilitates collaborative individual and business efforts, enhances the ideals of social responsibility, and promotes social action to achieve improved health for a world-wide community. This year Dr. Oswald Steward was present to address the runners and explain the importance of funding from community members. Without private funding many new cutting edge ideas would go unexplored. Millions of people worldwide live with the consequences of spinal cord injury and other disorders affecting the spinal cord. Research helps to offer hope to so many who need to believe in a better tomorrow. Dr. Steward’s grandson Tristan ran in his first 10K and placed 3rd in his age group!

The largest contributors this year were A Runner’s Zone with Asics, Signature Commercial Floor Covering, Wholesome Choice, Yorba Linda Water District and Griffith Printing. Wholesome Choice not only donated oranges and bananas, but also sent staff to prepare and offer the goodies. What’s best is they had fun doing it and have already committed to a return next year! They were such a tremendous help. Yorba Linda Water District (YLWD) provided ice cold water with souvenir bottles ready for each of the participants as they came off the course. YLWD has provided this service with their staff in attendance each year since the beginning, when the race was originally on New Years Eve morning. A Runner’s Zone not only sponsored our event for the second year, but held the packet pick up in the store so it was convenient for our local participants. Overall winners received a pair of Asics shoes and 2 tickets to the OC Fair Block Party, donated by OC Fair and Event Center. Griffith Printing donated multiple signs to help give direction to our participants. Not only did they help direct the crowd, they were beautifully finished with extra TLC for the cause. The owner of Griffith Printing is Ron Griffith who MC’d the event with Commander Chuck Street. They both did a superb job, had our event organized and in control! We hope they will join us next year and keep the event at the most professional level. The crowning glory door prizes were golf for two at Blackgold Golf and dinner at The Summit House Restaurant.

The day was well organized and enjoyed by racers and spectators alike. All proceeds for this event go to the Reeve-Irvine Research Center/Research for Cure, whose efforts are dedicated to advancing treatment for spinal-cord injuries and other debilitating neurological diseases. Please continue the tradition and run with us next year to support this important cause and help keep yourself healthy on Thanksgiving morning. For more information on next year’s race stay tuned to http://www.plymouthrocknrun.com/new/or contact Plymouth Rock N Run at 714-973-6615.
Raise money for Spinal Cord Research and the Reeve-Irvine Research Center by throwing yourself out of a perfectly good airplane this December!

Between December 26 - January 2 of this year, Skydive Perris is hosting a fundraising event teaming up with Research for Cure, a 501(c)3 Non Profit Organization and Cure the Cord, to raise money for Spinal Cord Research through the Reeve-Irvine Research Center at the University of California in Irvine. Skydive Perris is inviting brave participants who raise money for Research for Cure, to make a skydive as a thank you for raising this money!

For Indoor Skydiving (two flights in our indoor skydiving simulator), participants must raise a minimum of $99. Kids, 3 + years old can fly too!

For Tandem Skydiving, participants must raise a minimum of $250.00.

For both Indoor and Tandem Skydiving, participants must raise a minimum of $340.00.

Wednesday, Dec. 29th at 5pm. Spinal Cord Research evening fundraiser- Dinner, cash bar, guest speakers, live music, live auction, raffle and more! Cost for the evening is a minimum donation of $25.00...all proceeds go to Spinal Cord Research!

Join us at Skydive Perris this December during our Holiday celebration and make your indoor or outdoor skydive for a great Cause!

SIGN UP at www.skydiveperris.com or call 951-657-1664

THANK YOU from Research for Cure, Cure the Cord and the SKYDIVE PERRIS team!
Determined
to Never
Give Up

This year marked the fourth year for the Race for Tara Classic at beautiful Northstar Resort in Lake Tahoe. The Race for Tara Classic is named for professional mountain bike racer Tara Llanes, who was injured in a race in September 2007 and remains paralyzed from the waist down. Tara realizes that extreme sports have risks and she shows great determination in her ability to continue participating in them and in her own rehabilitation, as well as trying her best to give hope to others who suffer from paralysis. She is extremely driven and a well known racer, but surprisingly very humble. She continues to be grateful to the numbers of people who show up to make her race so successful.

Despite the rain, hundreds of racers showed up to race and show their support for Tara and to raise funds to support spinal cord injury research. The Reeve-Irvine Research Center is proud to be chosen by Tara as one of the groups to benefit from her event which continues to build quite a following.

“I would like to thank Northstar and all their staff, our entire TLC Crew and volunteers, the Reeve-Irvine Research Center for bringing both their doctors and their support, to Giant Bicycles, Shimano, Fox Shox, Sierra Nevada, Leatt Brace, Michelin, and Santa Cruz. We also have got to thank each and every racer that came out and competed even if there was a little rain and a little mud! Without you guys there wouldn't be a race, period.” --Tara

The Race for Tara Classic was a huge success this year with over a dozen bike industry sponsors and retailers and a record number of racers and volunteers. Her event has become well known in the mountain biking community attracting racers worldwide. It also includes a raffle of high end bikes and biking equipment all generously donated by her sponsors. The Northstar Resort proves to be an ideal location for the race. It is not only gorgeous but it hosts some of the most premier mountain biking trails in the area.

“Let's keep working towards curing paralysis and also building a fund for riders with catastrophic injuries. The Tara Llanes Classic is here to stay and as far as we’re concerned together the sky's the limit! See you next year!” --Tara

The Race for Tara Classic event has a tradition of being filled with more than just races. There are plenty of fun activities including the infamous raffle and extreme biking video. This year’s movie premier was “Life Cycles” a spectacular story of the bike, from its creation to

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its eventual demise, showing breath taking seasonal shots and incredible biking stunts. There was also a happy hour, a group BBQ and even a race for the kiddies. This year was the first to include children and to Tara’s surprise, 16 kids arrived geared up and ready to race!

This year we were excited to have Reeve-Irvine’s own Dr. Suzy Kim and Rafer Willenberg, a researcher from Dr. Oswald Steward’s laboratory race in the event. All of us at the Reeve-Irvine Research Center would like to thank Tara, her team of volunteers and the numerous sponsors that continue to help fund important spinal cord injury research and we all look forward to the next race. Stay tuned for more information on our web site www.reeve.uci.edu and watch the Spinal Connections newsletter or check out Tara’s web site http://www.racefortara.com/ for more information!
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.

Christopher and Dana Reeve

Ways To Give

**Outright Gifts**
Outright gifts, such as cash, securities or other property provide the Reeve-Irvine Research Center with much needed financial assistance. Outright gifts, be they large or small, have an immediate impact on projects because they can be used to support novel cutting edge research that will lead to new federal or state funded grants.

**Gifts of Endowment**
A gift of endowment is a fund that is maintained in perpetuity, a portion of the annual investment return is used for the purposes specified by the donor. The rest of the investment yield is returned to principal. Endowments provide a stable base of support for the Center's research efforts. Such endowments, which typically bear the name of the donor or donors, reflect your interest and serve as an enduring testament to your generosity.

**Gifts with Retained Interest**
Your gift can allow you to hold an interest in that gift for your lifetime or for a specified term of years. After that time, the funds become available to the specified project or program. For example, you can set up a charitable trust for a specified period, or for life.

**Planned Giving**
Planned gifts are gift arrangements that have tax advantages and often include lifetime income to a beneficiary or beneficiaries named by the donor. Many UCI donors have utilized planned giving methods and are enjoying the benefits today: capital gains tax savings, increased income and income tax savings.

**Appreciated Securities**
A gift of long-term appreciated marketable securities helps you save taxes twice. Such a gift will prove an income-tax charitable deduction and capital gains tax savings.

**Gifts of Real Estate**
When you give a gift of your home or real property, you may claim an income-tax charitable deduction based on the full market value of the gift, avoid capital gains taxes, and eliminate certain costs associated with the transfer of real property. Gifts of real estate can also provide income to you.

**Gift Pledges**
A pledge is a formal statement of intention to make a gift. It may be followed by an immediate gift or may simply confirm your intention to make a gift in the future. Many donors choose to complete their gift pledge by making regular payments over a period of time.

**Unrestricted Gifts**
When you do not restrict the use of your gift, the Center gains flexibility not otherwise available. The unrestricted gifts can be used to meet the changing or urgent needs at the Center.

Should you have questions or if you would like to receive more information on giving, please contact: Tania Cusack at (949) 824-5925 or e-mail tcusack@uci.edu
CONGRATULATIONS TO MELISSA STRONG: ICTS RESEARCH LEADERS OF THE FUTURE FELLOWSHIP RECIPIENT
The UC Irvine Institute for Clinical and Translational Science (ICTS) has awarded 3 pre-doctoral (TL-1) training awards program under the new NIH-funded Clinical and Translational Science Award (CTSA). The “Crossing Boundaries” training program is designed to integrate training in clinical research and translational science into the core curriculum of students in medicine, public health, nursing, pharmaceutical sciences, biomedical and social sciences, physical sciences, engineering, and informatics. Melissa, a researcher in Dr. Oswald Steward’s laboratory submitted a proposal entitled: Identifying the source of resistance to excitotoxic cell death in a mouse strain that is otherwise highly vulnerable. In this proposal we focus on two experimental objectives: to characterize induced resistance to excitotoxic cell death, and to identify genes that are differentially expressed in mice that develop resistance to excitotoxic cell death. The preliminary evidence that there are genes, or changes in gene expression, that can confer protection against neurodegeneration leads us to pursue molecular mechanisms that can be targeted for therapeutic intervention. The Reeve-Irvine Research Center would like to congratulate Melissa on this accomplishment and would like to recognize her for her research accomplishments.

JENNIFER YOUNAN RECEIVES SUPERIOR PRESENTER AWARD
Sigma Xi, the Scientific Research Society, held its Annual Meeting and International Research Conference on November 11th-14th in Raleigh, North Carolina. The theme of this year’s symposium was Food Safety and Security and its goal is to bring together students, scientists, and Sigma Xi members from North America and abroad. The student research conference allows for up and coming students to showcase their research and connect with esteemed scientists. Jennifer Younan, a senior at the University of California, Irvine, was one of 300 high school, undergraduate and graduate students invited to present their research at this conference. Jennifer is an undergraduate researcher at the Reeve Irvine Research Center whose work focuses on the excitotoxic effects and neurodegeneration of mice carrying a Huntington’s disease transgene. Under the guidance of Advisor Oswald Steward and Ph.D. candidate and mentor Melissa Strong, as well as UC Irvine’s Minority Science Program, Jennifer showcased her poster titled, “Time course of neuronal death following quinolinic acid treatment in mice carrying a Huntington’s disease transgene.” She was awarded Superior Presenter, the highest award given to only 38 individuals in attendance, and invited to join the Sigma Xi Society as an Associate Member. We congratulate Jennifer on her accomplishments and encourage her continued dedication to her research.

CALIFORNIA STEM CELL SAB CHAIRMAN, HANS KEIRSTEAD, WINS 2010 MATHILDE SOLOWEY LECTURE AWARD IN THE NEUROSCIENCES

Prestigious award given for outstanding work in the field of neuroscience. (Cited from California Stem Cell News and Events)
IRVINE, Calif. (February 25, 2010) UC Irvine neurobiologist Hans S. Keirstead has been named the winner of the prestigious Mathilde Solowey Lecture Award in the Neurosciences for 2010, an annual award administered by the Foundation for Advanced Education in the Sciences given to a researcher for outstanding work in the field of neuroscience. Keirstead will travel to the National Institutes of Health's campus in Bethesda, MD., to deliver the annual award lecture on May 18, 2010. The Mathilde Solowey Lecture Award in the Neurosciences was established in 1974 by Solowey, a microbiologist and longtime administrator at the National Institute of Neurological Disorders and Stroke, upon her retirement. It is intended to award a neuroscientist who is on a rising trajectory, and whose work is translational in nature. Past winners have gone on to become leaders of the neuroscience field.
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 Cusack at (949) 824-5925 or e-mail tcusack@uci.edu.

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

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

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

Check out our new and improved website!

SCI Clinical Database for California Residents

Not just a statistic! The Reeve-Irvine Research Center has created a SCI database to identify the number of people in California who are living with a SCI. Learning about your medical condition, employment, and recreational activities will allow us to improve access to specialized rehabilitation, SCI specific health care and support SCI research. Also, it will allow us to readily contact you for participation in ongoing clinical research and future clinical trials most appropriate for you.

You may qualify if:
♦ You have a spinal cord injury
♦ You currently live in California

Please contact Dr. Suzy Kim at rirc@uci.edu or call 949-824-3993 for more information on how to enroll in our database. All of your personal and medical information will be kept strictly confidential.

IMPROVED WALKING AFTER INCOMPLETE SPINAL CORD INJURY

If you have been living with a SCI for more than one year and are able to walk short distances, you may be eligible to participate in this study.

You will receive a functional MRI scan of your brain to help us understand the effects of rehabilitation on improving your ability to walk. All information obtained will be strictly confidential.

For more information please contact:
Kelli Sharp, DPT or Dr. Suzy Kim at sci@uci.edu or call 949-824-5145.