Number 27, Summer 2015

Reeve-Irvine Research Center Publication

Spinal Connections

Dr. Oswald Steward

CST Regeneration in the chronic injury setting!

As most of our readers know, the "Corticospinal Tract Regeneration Project" has been the focus of the Steward Research Group for years, and for the last 5 years has involved a multi-investigator collaboration that has been following up on a paper the team published in 2010. The original paper, published in Nature Neuroscience, showed that it was possible to induce regeneration of the corticospinal tract (CST) following spinal cord injury by deleting a gene called phosphatase and tensin homolog (PTEN). The latest papers from the Steward lab, published in 2014 and earlier this year, showed that CST regeneration was accompanied by recovery of motor function (see article by Sam Maddox on page 2 of this newsletter).

In a new breakthrough, our collaborator Dr. Kai Liu, who was first author on the Nature Neuroscience paper and now has his own lab at Hong Kong University, published a very important paper showing that is possible to induce CST regeneration in the chronic setting either 4 months or 1 year after a spinal cord injury!

The paper appeared in the July issue of the flagship journal of our field, the Journal of Neuroscience, and was featured on the cover. In the study, Dr. Liu used the same genetic deletion strategy that was used in the original paper. Mice received spinal cord injuries and then 1 year later, received an injection of a viral-based vector into their cortex, which produces a protein that deletes PTEN from the nerve cells that give rise to the CST. After deleting PTEN, CST axons regenerated past the injury and formed new connections.

The discovery that regenerative ability can be rebooted even 1 year after an injury greatly extends the window of opportunity for regenerating connections in the injured spinal cord. Next steps will be to determine if the regeneration is accompanied by reversal of paralysis.

RRC Reeve-Irvine Research Center

University of California, Irvine

PTEN Deletion Post SCI Regeneration and Recovery

by Sam Maddox
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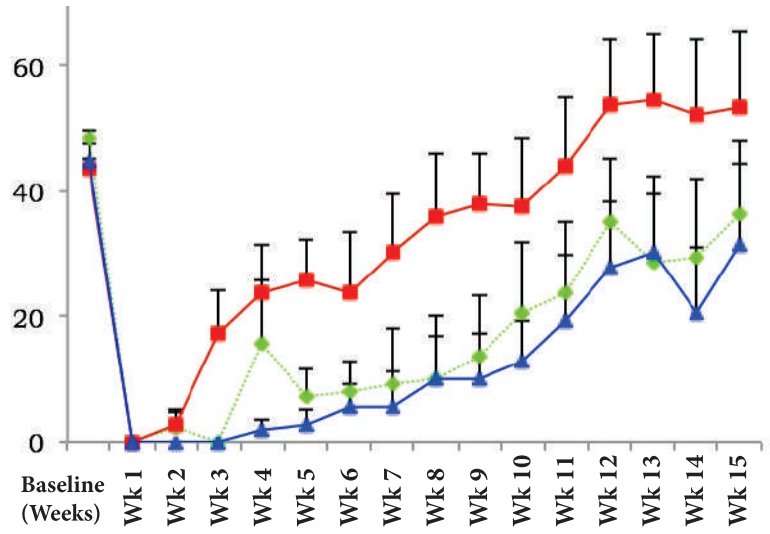
Christopher and Dana Reeve Website

Over the last few years we have written several times about a nifty genetic manipulation that reboots key nerves in the spinal cord to regenerate in a big way. Starting back in 2008, Zhigang He, at Harvard, got damaged optic nerves going again by deleting PTEN, a tumor suppressor gene that cancer researchers had come across back in the 1990s; this enzyme acts as a sort of brake when axons attempt to regenerate after injury.

In the world of cancer, of course, the idea is to keep the growth brake on; in spinal cord repair, it's just the opposite. Anyway, in later experiments, when PTEN was removed, the corticospinal tract (CST) regenerated in lab animals – important because the CST comprises crucial wiring for arm and hand function.

The most recent research, from Camilla Danilov and Oswald Steward at the Reeve-Irvine Research Center at the University of California, Irvine, takes a big step toward clinical relevance. In all previous experiments, animals used in the tests had PTEN deleted before they were spinal cord injured. This time, they took the PTEN brakes off after animals had been paralyzed.

The paper, out in the journal Experimental Neurology, is titled "Conditional genetic deletion of PTEN after a spinal cord injury enhances regenerative growth of CST axons and motor function recovery in mice."



Improved recovery of hand function in rats due to PTEN deletion: red=animals with PTEN deletion; blue and green=two untreated control groups

From the abstract:

Previous studies indicate that conditional genetic deletion of phosphatase and tensin homolog (PTEN) in neonatal mice enhances the ability of axons to regenerate following spinal cord injury (SCI) in adults. Here, we assessed whether deleting PTEN in adult neurons post-SCI is also effective, and whether enhanced regenerative growth is accompanied by enhanced recovery of voluntary motor function.□□These results indicate that PTEN deletion in adult mice shortly post-SCI can enhance regenerative growth of CST axons and forelimb motor function recovery.

The new study used a gene delivery vector to delete PTEN 20 minutes after a moderate contusion injury at C5. The animals without PTEN could grip and grasp much better than control (injured but untreated) animals.

Why this injury model? From the paper:

...the injury model used in this study was a moderate cervical contusion at C5 centered on the midline of the spinal cord that produced bilateral tissue damage and bilateral function deficits. We chose this injury model for its human relevance. More than 50 percent of spinal cord injuries are at the cervical level, impairing both lower and upper extremities and the most common type of injury in humans is the contusive type.

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Reeve-Irvine Research Center

Induced pluripotent stem cells:
A recent discovery that could lead to personalized medicine for SCI

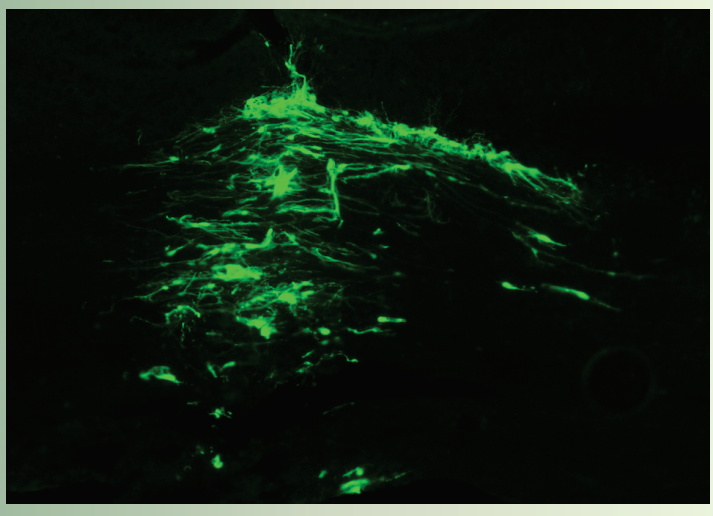
My name is Joe Bonner and I am a postdoctoral fellow in the lab of Dr. Steward at the Reeve-Irvine Research Center and I study the use of human neural stem cells for the treatment of spinal cord injury and my work is currently funded by the California Institute for Regenerative Medicine (CIRM) through a training grant administered at the Bill and Sue Gross Stem Cell Center here at UCI. Stem cells are a special type of cell that have the potential to repair tissue by replacing cells that were lost due to spinal cord injury. Stem cells are present in the brain and spinal cord and they contribute to the normal function of the nervous system throughout life. In the event of a spinal cord injury, resident stem cells respond and make an attempt to repair the damage but there are simply not enough stem cells to fix such serious injuries. In my research, I transplant neural stem cells in an effort to improve tissue repair and to restore the neural connections between the brain and the body. In addition to transplants of stem cells I also administer "growth factors" to improve the function of the transplanted stem cells and at the same time I also manipulate the function of the PTEN/mTOR pathway, which Dr. Steward has previously shown can give the injured nerve cells in the spinal cord a regenerative boost. The goal of my work is to understand how stem cells can contribute to the repair of spinal cord injury and to ultimately create a treatment for people who have suffered a spinal cord injury.

The human neural stem cells that I use in my research are made from a relatively new kind of stem cell called induced pluripotent stem cells, or IPS cells. IPS cells were first described in 2006 by Shinya Yamanaka, who won the Nobel Prize for the discovery in 2012. In the short time IPS cells have been around scientists have begun to understand how they could be applied to treat illness and injury. IPS cells have many characteristics that make them an interesting resource in our search for a treatment for spinal cord injury.

IPS cells are made by "reprogramming" or "inducing" an adult cell to become a stem cell. This means that stem cell scientists are able to take a common cell found in an adult, such as a skin cell, and to change that skin cell into a stem cell. This procedure eliminates many of the difficulties that are associated with embryonic stem cells while producing a stem cell with many of the same characteristics. The most intriguing benefit of IPS cells is that they could be made for each individual patient. If an IPS cell therapy was designed to use a patient's own cells then there would be no need for the patient to take additional medications to prevent an immune reaction or transplant rejection.

IPS cells have the potential to make any cell in the adult body, including the cells that make up the spinal cord and brain. IPS cells can be grown for a very long time in a culture dish. This means that cells can be expanded from a small number into enough cells to conduct experiments and to eventually treat human patients. Before IPS cells were discovered, the only type of cell that had these characteristics were embryonic stem cells. Although embryonic stem cells (ESCs) may prove useful for treatment of spinal cord injury, ECS's are not "personalized" so patients who receive ESC transplants have to take immunosuppressant drugs to prevent rejection.

I have been able to demonstrate that human neural stem cells derived from IPS cells can survive in the injured spinal cord and make nerve cells (neurons) and support cells (glia) after transplantation. My continuing research seeks to determine if these transplanted stem cells can communicate with injured nerve cells in the injured spinal cord and if those lines of communication can improve the recovery of function in an animal model of spinal cord injury.



Human neural stem cells transplanted into the injured mouse spinal cord. Transplanted stem cells are engineered to express green fluorescent protein to make them easier to see after transplantation. Image was taken at 60x magnification.

REEVE–IRVINE RESEARCH CENTER

2015 Annual Symposium
held February 6, 2015

Stem Cells for the Injured Spinal Cord

The RIRC hosted an exciting symposium on February 6 focused on stem cell based therapies for spinal injuries like SCI and ALS, with special focus on both the success and failures of various therapies. We brought together experts that have made significant contributions in these areas and many of our speakers have either been involved in previous clinical trials or are currently involved in therapies that have great potential for clinical applications in the very near future. The target audience for this symposium consisted of MD's and RN's in Neurological Surgery, Emergency Medicine, Physical Medicine and Rehabilitation and Orthopedic Surgery. Additionally the target audience included Ph.D.'s in Neurology, Anatomy & Neurobiology, Bioengineering and Translational Sciences.

The objective of the symposium:

- Identify stem cell based therapies being used for degenerative disorders to patients and the community.
- Determine some pitfalls of current stem cell based therapies for degenerative diseases and establish ways to improve future clinical trials/studies.
- Identify any possible outcomes (physical, mental, etc.) that may result from the use of these stem cell based therapies

Course Director

Dr. Oswald Steward

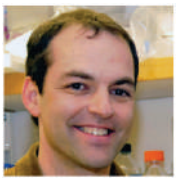
Director, Reeve-Irvine Research Center
Professor, Anatomy and Neurobiology,
University of California, Irvine

Distinguished Speakers

Eva Feldman, M.D, Ph.D

Director, Program for Neurology
Research and Discovery
University of Michigan

Intraspinal stem cell transplantation in ALS: Clinical trials update



Philip Horner, Ph.D

Department of Neurological Surgery
University of Washington

Safety and success of induced pluripotent stem cells delivered to the injured spinal cord

Lyn Jakeman, Ph.D

Program Director,
Repair and Plasticity Cluster
NIH-NINDS

Embryonic spinal cord transplants: An historical perspective

Continued on facing page

Thomas Lane, Ph.D

Department of Pathology
The University of Utah

Human neural precursor cells promote neurologic recovery in a model of demyelination

Jane Lebkowski, Ph.D

President of Research and Development
Asterias Biotherapeutics Inc

Development of hESC-derived oligodendrocyte progenitor cells for the treatment of spinal cord injury

Martin Marsala, Ph.D

Department of Anesthesiology
University of California, San Diego

Spinal stem cell replacement therapy for the treatment of traumatic spinal cord injury

Mark Noble, Ph.D

Department of Biomedical Genetics
University of Rochester Medical Center

Promoting CNS repair and protection via repurposed small molecules and metabolic regulation

Christoph Pröschel, Ph.D

Department of Biomedical Genetics
University of Rochester Medical Center

Multimodal astroglial cell therapy for CNS injury and disease

Scott Whittemore, Ph.D

Department of Neurological Surgery
Kentucky Spinal Cord Injury
Research Center

Is the biology of stem cells grafting in SCI compatible with the regulatory issues?

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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University of California, Irvine

PTEN Deletion
Continued from page 2

Another thing the scientists wanted to know is if this technique would give the CST axons a boost. The answer is yes, although for reasons that are not clear, CST growth is less than in previous experiments. From the paper:The regenerative growth seen here resembles what has been previously reported following spinal cord injury ... The extent of the regenerative growth appears less extensive, however, although direct comparisons are difficult because the site and nature of the injury are different (C5 contusion vs. T8 dorsal hemisection or crush). Further studies will be required to address this issue.

In conclusion, the present study demonstrates enhanced recovery of forepaw gripping and grasping function and enhanced regenerative growth of injured CST axons with conditional genetic deletion of PTEN in adult mice shortly after a spinal cord injury. These results suggest that manipulations of PTEN or the downstream mTOR pathway may be a viable target for therapeutic interventions to promote axon regeneration after spinal cord injury.

Meet the Scientists Forum

The annual Meet the Scientists Forum was held on March 14th at the Reeve-Irvine Research Center and was choc full of guest speakers specializing in SCI research, demonstrations of new technologies and some insightful discussion about the latest news in spinal cord injury research.

Visiting scientists included:

Jerry Silver, Professor of Neuroscience from Case Western University, is back by popular demand to Meet the Scientists. Dr. Silver discussed the latest research on functional regeneration beyond the glial scar. Dr. Silver published a major paper in the journal Science in December 2014 describing a novel peptide that improves regeneration after spinal cord injury.

Brian Kwon, Professor of Orthopedics, Spine Surgeon, University of British Columbia and the International Collaboration on Repair Discoveries (ICORD). The focus of his discussion with our guests was on his leading a national clinical trial in acute SCI to establish biomarkers of injury. This multi-investigator clinical trial aims to improve guidelines for the management of patients in the early stages of their injury, and develop a more complete picture of the pathophysiology of acute human SCI.

Maya Hatch, VA Advanced Fellow at the Veteran Affairs Healthcare System and Dr. Sujin Lee, Department of Physical Medicine and Rehabilitation, UCI. Drs. Hatch and Lee provided demonstrations of braces that are being tested to reduce lower back pain.

Suzy Kim, M.D. Rancho Los Amigos Hospital and Rehabilitation Center. Dr. Kim, formerly at RIRC, provided wheelchair fitting consultation. Dr. Kim was also available to answer questions regarding rehabilitation and SCI.

After surveying past attendees from previous forums we learned that our guests preferred to have more one-on-one time with our researchers and to see direct demonstrations of research projects underway. This year we made that happen and these world renowned researchers spent the bulk of the forum talking directly to those who attended in order to answer burning questions about spinal cord injury research. The event was a great success and we hope that you will join us next year!

You can see video of the demonstrations and discussion on video if you were unable to attend by visiting our newly redesigned website at www.uci.edu

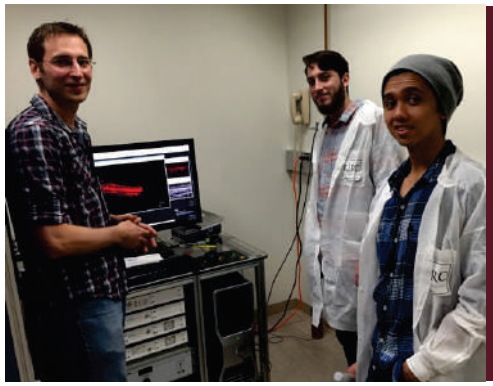
PLANNED GIVING

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

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

RIRC Outreach Lab Tours

This past spring/summer the RIRC hosted several lab tours where students were able to learn about spinal cord injury research. These tours consisted in learning what our research lab does and what our goals are. They looked at brain and spinal cord images through our two photon and electron microscopes, and they heard about ongoing projects being conducted by our postdoctoral fellows.



On Friday March 20th we hosted a group of fifteen students coming from Fullerton and Santa Ana Community College as part of UCI's Minority Science Programs housed in the Ayala School of Biological Sciences. This visit was supported by the Bridges to Baccalaureate Program funded by NIH; which seeks to advance the careers of students who are interested in pursuing a biomedical research career. Following their participation in the Bridges Program, many participants enroll at UCI in programs in the biomedical sciences. As a matter of fact, two students that participated are currently volunteering in the lab.

In July and August we hosted students as part of the UCI Center for Educational Partnerships (CFEP) program headed up by Dr. Darlene Boyd, with Rebecca S. Craft, M.Ed.S. as instructor. One group was part of the UCI Gifted Student Academy, which offers unique residential and commuter summer programs for gifted students on the UCI campus.

We also welcomed twenty high school students and six chaperones from Qatar for an immersion experience in STEM. These students attend different high schools in Qatar and have varied interests in science-based emerging technologies.

It was a pleasure hosting these students. It's a wonderful opportunity for gifted young scholars to expand their knowledge in areas of interest, and to have opportunities for accelerated learning.

CHRONIC PAIN CAUSES BRAIN INFLAMATION. WHY SHOULD YOU CARE?

Research Findings:

Pain is a multidimensional experience, and how much the pain is 'bothersome' significantly impacts the quality of life of the sufferer. In fact, the emotional component of pain has been argued to be a great metric in measurements of quality of life. There is extensive interaction between systems involved in pain processing and brain regions responsible for mood. Notably, chronic pain co-exists with depression, which is thought to involve imbalance in a brain system that uses the neurochemical dopamine. Dr. Cahill recently published a paper in Journal of Neuroscience (available as a free open access article at http://www.jneurosci.org/content/35/22/8442.long) that neuro-inflammation, as the result of ongoing pain caused by nerve damage (neuropathic pain), occurs in brain regions important for reward and mood. Reward circuitry is important for how we feel (mood), our motivation, and our ability to feel pleasure. Her research team identified that non-neuronal brain cells, called microglia, alter brain activity important for producing reward. This research identifies a pathway from microglia to neurons that causes suppression of the neurochemical dopamine and thus likely contributes to many of the devastating sequelae of chronic pain, including the poor response many pain patients have to their opioid prescription medications, debilitating affective disorders, and substance abuse (Figure 1). Her research is supported by the recent clinical trial that reported minocycline, a microglial inhibitor, did not alter pain intensity, but diminished how bothersome pain is in patients with neuropathic pain. This publication was recently picked up by multiple media sites including the OC Register (Wednesday, June 17th) as well as various websites including: MD magazine, Free Press Journal, Medical News Today, Neurology Advisor and Psychiatry Advisor.

Why is this research important?

Approximately, 20-25% of Americans suffer from chronic pain making it the most common form of chronic illness under the age of 60. The Institute of Medicine estimates that it costs our society $635 billion spent per year. Treating non-cancer chronic pain is a challenge for physicians because many patients do not respond to typical analgesics, such as ibuprofen-like drugs or opioids such as morphine. Additionally, treating patients with opioids long term has been come controversial because of the high incidence of addiction to pain medications, and there are studies questioning the effectiveness of opioids for treating certain types of chronic pain, especially those of nerve injury origin. Dr. Cahill's study imposes a paradigm shift in the field of chronic pain because it identifies that chronic pain can cause neuro-inflammation in brain regions important for reward experiences. The work identifies novel signaling and biophysical mechanisms by which microglia alter neuron activity in reward circuits, important for mood, motivation, and pleasure. The impact of our research is not restricted to the problem of pain, but is broadly relevant to mood disorders such as depression and substance abuse. Both of these medical conditions are associated with disruption of reward circuitry. Chronic pain patients are more than twice as likely to suffer anxiety and depression, and co-existence of pain with mood disorders is reported to be 30-100% depending on the causes of chronic pain. Importantly, chronic pain is second only to bipolar disorder as the major cause of suicide among all medical illnesses. Dr. Cahill's study suggests that treatments that target neuroinflammation will be an important novel therapy to alleviate many of the troubling emotional sequelae of chronic pain. Our study also has implications for why some chronic pain patients become addicted to their opioid analgesics used for managing chronic pain.

Next steps:

There are many directions for this research. First, we would like to establish that the circuitry changes account for affective-like behaviors. We have a novel compound from Dr. Yves De Koninck that has the potential to restore function and normalize reward-like behavior. Once these compounds get approval for clinical trials, we will test whether restoring reward function is therapeutic in a chronic pain population. We would also like to follow this up with clinical research pursuing imaging studies to identify whether chronic pain patients also show the same disruption in reward circuitry.

Take-home message.

Chronic pain is a devastating disease that negatively affects a person's quality of life. Not only do patients have to live with pain everyday; they also commonly suffer from depression. Our studies show that chronic pain changes your brain in areas important for mood. Importantly, we provide proof that the prevalence of depression in chronic pain patients is likely an organic disease and is not psychological. The work indicates that changes in the brain caused by pain likely cause this mood disorder; depression is not simply a consequence of their state of mind from having to live with pain. We have identified multiple proteins that can be targeted for translational medicine to determine their effectiveness in improving quality of life for those suffering from chronic pain, as well as potentially for Major Depressive Disorders. Our research identifies a pathway that likely contributes to many of the devastating sequelae of chronic pain, which include the poor therapeutic response of opioid analgesics in a subset of chronic pain patients, debilitating affective disorders and substance abuse.

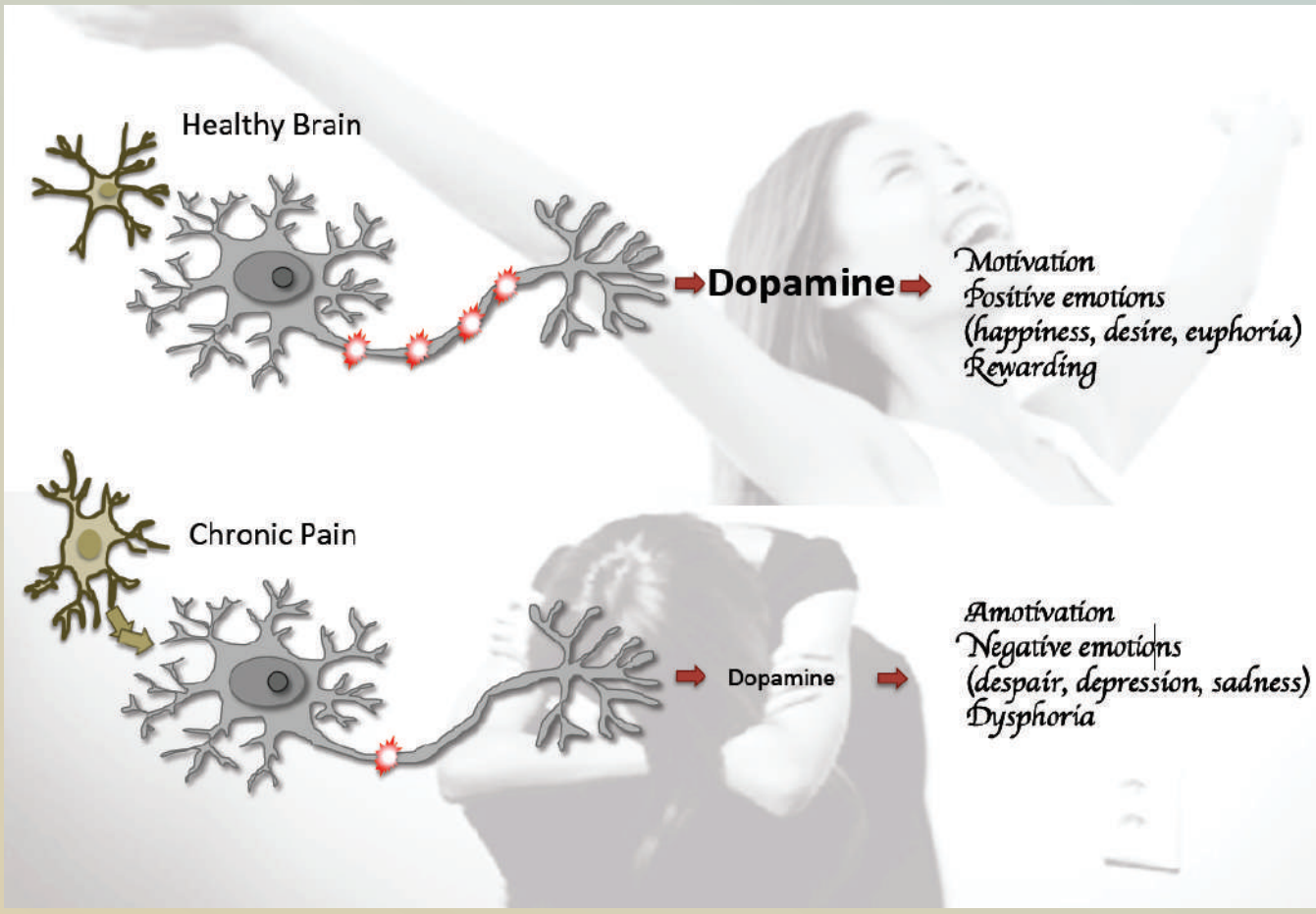


Figure 1. In a healthy brain dopamine neurons in a brain region called the ventral tegmental area release dopamine in many parts of the brain. Activation of these neurons produces pleasurable experiences to natural rewards such as food and sex, as well as to drugs such as cocaine and morphine. Chronic pain causes disruption of these neurons. Neuropathic pain (pain caused by damage or dysfunction of the nervous system) generates a neuro-inflammatory response in the ventral tegmental area. This is evidenced by activation of microglial cells (resident immune cells in the brain) in this brain region. These immune cells release factors that result in decreased activity of dopamine neurons. This reduced activity is associated with feelings of despair, depression and an overall suppression in the ability to experience pleasurable emotions.

The Legacy of Frank Freed

It is difficult to say goodbye to our dear friend and supporter of our Center. On April 22, 2015 Frank Holston Freed who was born on September 17, 1924 passed away due to congestive heart failure. He is survived by his wife Evelyn Freed who has generously supported the RIRC since its inception. Frank enlisted in the Army in 1942 and was a soldier in World War II losing his arm in France. Frank graduated from Wheaton College in 1948 with a BA Degree in Philosophy and from Fuller Theological Seminary with a BD Degree in Theology. He was the pastor of Bethany Baptist Church in West Covina, California from 1951-1957. He received an MA Degree in History from Stanford University in 1958, and was a founding Pastor of Valley Church in Cupertino, California from 1959-1969.

Frank received a Secondary Teaching Credential in History at USC in California in 1970, and then went to Fuller Theological Seminary School of Psychology where he earned a Ph.D. Degree in Psychology in 1974. Frank was a Clinical Psychologist in private practice in Orange County, ending his career as Director of Counseling at the Crystal Cathedral for ten years until his retirement. In 1997 Harold Shaw Publishers published Frank's book "Breaking Free When You're Feeling Trapped". He also published another book titled "Breaking Free" about bettering your life through attitude. He was credited with making a positive impact on many people's lives with his loving spirit and educational counsel. The generosity and support that Evelyn and Frank have given to our Center over the years has made a lasting impact on spinal cord injury research efforts. Frank has left a very large footprint and will be sorely missed by us all at the Reeve-Irvine Research Center.

Upcoming Symposium

The RIRC is pleased to announce that Mark Tuszynski is the winner of this year's Reeve-Irvine Research Medial".
The Reeve-Irvine Medal Symposium will be held in his honor on November 5th, 2015

FRANK FREED MEMORY FELLOWSHIP:

Please consider helping us with a donation to establish the "Frank Freed Memory Fellowship". The name is a double entendre; the fellowship is to honor Frank Freed via a fellowship for research on memory. For more information, see our website or contact Tania Jope.

Join us for the Plymouth Rock 'n' Run 5k/10k/walk/kids fun run Thanksgiving Morning

Registration for 2015 is open!!

New this year . . . .

- Expanded 5k age-group awards categories for teens and pre-teens
- Team Fundraising groups with prizes for the team that earns the most to help SCI Research
- 'Legacy Lite' program: Special awards recognition for those who will be 5k or 10k participants for three years running (2013 – 2015)

Register online today! **www.plymouthrocknrun.com**

Ways to Give....

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

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

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

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

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

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

Are you in the know?

The Reeve-Irvine Research Center now has the latest advances in spinal cord injury research published on our brand new website.

www.reeve.uci.edu

Hope is in research.
Ask yourself...how can I help?

Join us in the fight for cures today!

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Do you have hand or arm impairment after a strokeor spinal cord injury?

Volunteers needed for a study to improve hand and arm function after stroke and SCI

If interested, contact us at:
Phone #: 949-824-8423
Email: iMove@uci.edu
And ask about the "Music Glove Study"

NOW ENROLLING!

Purpose of Study:

- To investigate if therapy with simple rehabilitation devices can improve hand and arm function after stroke and SCI

About the Study:

- 4 visits to the University of California, Irvine over 8 weeks with trained therapists
- Therapy duration is 3 weeks and may occur at home or in the UCI Medical Center
- $20 compensation after each visit
- All equipment provided for your home therapy at no cost to you or insurance

Lead Researchers for this Phase III study:
An Do, MD; Department of Neurology and
Kelli Sharp, DPT; Department of Dance