Update on neuronal vitality with PTEN deletion

We reported in the last issue on Erin Gutilla’s paper on long-term consequences of PTEN deletion (Gutilla et al., 2016). The paper had just been released electronically, but at that time, we didn’t know that it had been selected as the cover image for the Journal. This is a nice highlight of our research!

Erin, who is an MD/PhD student, is completing her dissertation research in the spring. In addition to the paper above, she was invited to submit a review for the journal “Neural Regeneration Research”. This is another nice recognition of the impact and importance of her discoveries.

The review summarized our findings that deleting PTEN in young (or developing) neurons in the way that enabled axon regeneration didn’t seem to be harmful. Even more important, neurons lacking PTEN appeared more robust and healthy than other neurons more than 1 year after the intervention. Erin’s dissertation research is following up on this very interesting finding. She’ll complete her PhD research in the spring and then back to medical school. Look forward to further updates in our next newsletter!

A high magnification view of a PTEN immunostained section using phase-contrast microscopy from the brain of a mouse one year following neonatal conditional PTEN deletion in the motor cortex. Phase imaging was used to verify the presence of large layer V PTEN negative “ghost cells”, which appear blue in this image. Neighboring PTEN positive neurons are stained brown and are visibly smaller than the ghost cells.


Update on stem cell trials for spinal cord injury: The good, the bad & the ugly

In our spring newsletter, we reported on the results of the trial being carried out by the company “Asterias”, in which people who have suffered spinal cord injuries are receiving surgical injections of oligodendrocyte precursor cells (OPCs) derived from human embryonic stem cells (hESCs) into their spinal cords. The OPC trial was based on research carried out by Hans Keirstead at the RIRC, and the current trial is called the “AST-OPC1 SCIstar study”. On November 14, Asterias announced that enrollment in the trial had been accelerated with three patients having received cell injections in early November. In addition to the patient cohorts that previously received doses of 2 million and 10 million cells, two patients have now received the maximum dose of 20 million cells, which is thought to be roughly comparable to what the rats received in the initial study.

The two patients who received the 20 million cell dose are cervical AIS-A, meaning complete loss of motor and sensory function below the cervical injury site. AIS-B patients have similar cervical injuries and complete motor loss but retain some sensory function, and Asterias believes AIS-B patients may be particularly responsive to AST-OPC1 due to the larger amount of intact spinal tissue remaining at the injury site. The company plans to report 6 month efficacy and safety data in January 2017. The “AST-OPC1 SCIstar study” is an FDA approved trial that has been extensively reviewed by scientific and medical experts. The data from the trial will be fully analyzed and reported.

The carefully controlled and FDA approved clinical trial that Asterias is running is in stark contrast to literally hundreds of “Stem Cell Clinics” that are popping up all over the United States that deliver untested “stem cell” products to those who are able to pay. In September, the FDA held a 2 day public meeting on possible changes in rules for stem cell clinics in the United States. Surprisingly, there are few rules and little oversight of such clinics, raising concerns that clients may be getting noncompliant cell-based interventions.

Tighter regulations may not sound like a good thing, and some people came to the meeting to testify that they had benefitted from treatments they had received from stem cell clinics. On the other hand, FDA regulations are an important reason why we can trust that the medications and treatments that we receive (and pay for) have been tested for safety and effectiveness. Patient safety IS at stake, and very few of us can afford to pay tens of thousands of dollars for something that doesn’t work. The problem is that in an un-regulated market, it’s not possible for most consumers to distinguish between treatments that have been tested and shown to be safe and effective vs. treatments that have never actually been tested at all. As Dr. Larry Goldstein wrote in an e-mail: “Thoughtful FDA regulation of the growing stem cell industry is essential to help consumers distinguish fraudulent claims from legitimate clinical trials, research and therapy development”.

The other huge problem is that the term “stem cell” is now being used for a number of different cell types and treatments. Clinic websites advertise different products, but there’s no oversight or independent validation of claims that a particular product is actually what the clinic says it is. There’s no playbook that consumers can use to figure it all out.

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One of the important functions of the RIRC is training young scientists for research on spinal cord injury, nerve regeneration and stem cell applications. Our trainees then go on to positions at other universities or private companies, thereby expanding the spinal cord injury workforce. The most important metric is the success our training fellows have in taking their career in the direction they desire.

Accordingly, we are pleased to announce that two RIRC postdoctoral fellows have completed their training and been offered positions at other universities. Dr. Zack Gallaher has just been recruited to a faculty position at the University of Western Washington. Zack and his family come from Washington state and are thrilled to be returning to the area and their families there. In his time at RIRC, Dr. Gallaher carried out a comprehensive experiment to test whether manipulations of the PTEN gene would enhance regeneration of peripheral nerves in the same way that occurs with nerve connections (axons) in the central nervous system (CNS). Dr. Gallaher discovered that manipulations of PTEN did enhance regeneration of peripheral nerve, but not as extensively as in the central nervous system. A major research paper describing these studies is under review for publication.

Dr. Aminata Coulibaly will be completing her postdoctoral fellowship with Os Steward in January, and was offered a position as Research Associate at the University of Virginia. She will be moving to UVA in January to undertake studies on the specialized immune system that serves the brain. This is a new and exciting area of research launched in 2015 by the discovery of a brain lymphatic system. This discovery was a candidate for one of the top 10 discoveries of the year in 2015. Dr. Coulibaly’s research at RIRC focused on how nerve cells and glial cells responded to deletion of the gene PTEN in the cortex in the way that we have shown to enhance regeneration after spinal cord injury. She’ll complete her studies in January, but it is already clear that there are some very exciting discoveries that we will describe in detail in future Spinal Connections.

The Reeve-Irvine Research Center would also like to congratulate Dr. Patricia Salgado who completed her final requirements for her Ph.D. in August! Dr. Salgado’s Dissertation, entitled “Phosphorylation of ribosomal protein S6 as a mechanism to regulate translation at activated synapses” described novel molecular mechanisms of synaptic changes due to experience. A central theory of modern neuroscience is that changes in synapses due to activity are the way the brain stores memories. For example, brief patterns of activity actually change the structure of synapses, increasing their strength. Repeated activity patterns then reinforce the structural changes, and this underlies long-term memory. Patty discovered a fundamental mechanism underlying this process through which signals from synapses trigger molecular changes in the machinery that synthesizes proteins, specifically, small structures in the cell called “ribosomes”. These changes in ribosomes then change the types of proteins that are being produced at synapses. Our graduate researchers are an important part of our RIRC team please join us in congratulating Dr. Salgado and help us to recognize her for her research accomplishments.
The Move to Move Continues

In the winter of 2010 the RIRC announced the launching of the Cortico Spinal Tract PTEN Regeneration Project by Dr. Zhigang He from the Children’s Hospital, Harvard and Dr. Oswald Steward at the Reeve-Irvine Research Center, UCI. In this study, Drs. He and Steward devised a way to induce regeneration of a pathway that controls voluntary motor function after spinal cord injury. This is accomplished by blocking a naturally occurring human enzyme known as PTEN which enables unprecedented nerve regeneration. This study showed clearly that shutting off PTEN allows robust regeneration of the corticospinal tract, previously considered the most difficult tract to regenerate.

After learning of these advances the Wentz family decided to establish the “Z Fund” named after Zack Wentz who suffered a spinal cord injury at the age of 15 at a ski resort when the family was on vacation. The Wentz family described the following years as an emotional roller coaster and Zack was faced with learning to readjust his life from being a very active teenager to one who faced the challenges of living with paralysis from the chest down. The purpose of the Z Fund was to raise money for SCI research and the CST PTEN Regeneration project and raised close to $120,000 at Stanford University in 2010. In 2011 the Wentz family pulled together another event they called the “Move to Move” that raised over $100,000. These events were key in providing the funding to carry out critical studies that generated preliminary data for two NIH grants to Drs. He and Steward which allowed for an additional 5 years of research and yielded well over 1.5 million in research funding that otherwise would not have been possible.

Since the Z Fund was established in 2010, Zack worked at the Riekes Center for Human Enhancement as a piano teacher, teaching a wide variety of students how to play the piano by ear, just as he taught himself how to play the piano! Simultaneously he worked at a Mexican restaurant, as well as at a summer camp three consecutive summers.

He received word that he was accepted to the University of Southern California (USC), and was fortunate enough to receive a “Swim With Mike Scholarship”, a scholarship dedicated to providing financial resources for physically challenged athletes.

In 2014, Zack pledged and ultimately became an active member of Delta Omicron Zeta, USC’s leadership fraternity. He worked in the USC Athletic Department as an intern assisting in the development of the Heritage Association, an organization whose goal is to create a unified community among USC student-athletes and student-athlete alumni through philanthropy.

In 2015, Zack applied for the Lime Connect Fellowship program, to which he was ultimately selected as one of twenty fellows to participate in a highly competitive leadership and development program in New York City for students with disabilities. Additionally, Zack founded USC’s 1st Annual Wheelchair Basketball Tournament, an idea that he developed and included in his application to USC. The tournament has been a wild success each of its first two years, including participation from over 100 USC students, as well as participation from USC’s Men’s and Women’s Basketball Teams. Zack has already started preparing for the 3rd annual WBT this upcoming spring!

In the spring of 2016, Zack went through a grueling pledge process that culminated with his becoming a Trojan Knight, USC’s guardians of tradition. “The three pillars of our Trojan Knights organization are Brotherhood, Philanthropy, and Spirit. We are the guys who are front row at every football and basketball game with our chests painted. And we are the guys who put on numerous philanthropy events around the community, including USC’s biggest philanthropy: the big Swim with Mike Event in April”.

In the summer of 2016, Zach got a job as a social media and campus ambassador for a sports news company called The Lead Sports. He also started volunteering with Dharma Rescue, a volunteer organization dedicated

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Move to Move... From Previous Page

to rescuing disabled dogs and training them to become therapy dogs. Finally, this past fall semester, Zack inspired a position within USC’s Undergraduate Student Government and has held that position since. He serves as the Disability/Accessibility Issues Advisor on USG’s Board of Advisors. This position has had countless initiatives regarding how to make USC a more accessible place, and holding this position within USC’s Undergraduate Student Government has expanded Zack’s resources immensely, which has been conducive to more productivity with his initiatives. These initiatives range from improving accessibility (which covers all sorts of disabilities) in dining halls, dorms, and classrooms, to being a liaison and meeting with architects working on renovations for various USC sporting venues.

Zack did not let his challenges slow him down and neither have the research teams working on the CST PTEN Regeneration project. Since the initial launch of this project, the Steward lab published papers in 2014 and 2015 showing that CST regeneration was accompanied by recovery of motor function. And the latest new breakthrough discussed in a recent issue of our Spinal Connections that discusses collaborator Dr. Kai Liu’s first author article in Nature Neuroscience showing that it is possible to induce CST regeneration in a chronic setting! (see cover story of Summer 2015). This is the most promising finding in chronic regeneration that we have seen to date and we are all very excited about the future of this project.

We would like to congratulate Zack Wentz on his amazing accomplishments despite challenges that faced him, and thank the Wentz Family for showing that perseverance pays off! There is so much promise in the future of research that could help Zack and many others who could benefit from potential therapies stemming from research conducted at the RIRC. All of us are grateful to the many private gifts we receive that help propel these important projects forward.

If you are interested in supporting this project or the RIRC please visit consider giving on line at www.reeve.uci.edu, enclose your tax deductible check included in this newsletter or contact Tania Jope for more information at (949) 824-5925 or tania.jope@uci.edu

And there are more examples of some really ugly consequences. In July, the highly respected New England Journal of Medicine published a scientific report on a man who developed a tumor in his spinal cord after receiving infusions of different types of stem cells and a transplant of “fetal neural stem cells” into his spinal cord. (Berkowitz et al., 2016, Glioproliferative lesion of the spinal cord as a complication of “Stem-Cell Tourism” (http://www.nejm.org/doi/full/10.1056/NEJMoa1600188). The patient developed pain that got worse over time and increasing paraplegia. A biopsy of the tumor revealed a mass comprised of cells from another human being that were proliferative (meaning that the tumor was growing). This article concludes:

“The unregulated commercial stem-cell industry is not only potentially harmful to individual patients but also undermines attempts to study stem-cell therapies in clinical trials. This case provides further support for the conclusions of an article advocating increased investigation of commercial stem-cell clinics and increased patient education regarding the risks of stem-cell tourism. Such experimental treatments must be studied in a safe, regulated environment.”

So, as we’ve cautioned before, y’all be careful out there!

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
Trotting off the Turkey Tummy!

In its 9th year of fundraising for the Reeve-Irvine Research Center, Research for Cure’s Plymouth Rock ‘n’ Run team put on another successful 5k/10k Thanksgiving Day “turkey trot”, playing host to 2500 participants, exhibitors, and spectators. The event, held annually at Yorba Regional Park in Anaheim Hills CA, was established in 2006 by the Johnson family of Yorba Linda, who helped again this year securing sponsorships and prizes. Tim Johnson, co-founder of PRNR, was the start-line announcer for the 5k and 10k races and kicked off both with an inspiring speech before the starting horn was sounded.

This year’s finish line festival featured a silent auction, prize wheel for the kids, vendors selling gifts for the holidays and even a mobile tropical cage with numerous trained parrots! Family Tree Produce provided complimentary food at the finish line for the participants, and a special coffee booth open to all attendees was provided by Influence Church. Cure Medical helped to sponsor some of the cost for the event T-shirts for everyone who participated. Task Force Heroes again donated participant goodie bags and staffed gear check at the event.

We are so grateful to all those who donate their time and talent to make this event a huge success! Event managers James and Deborah Scott worked tirelessly as they have in years past to produce a well-organized race, with assistance from Michelle Laizure, as well as Travis Torres and his team from Bear Pit Gym & Fitness Center. Many other volunteers from local school organizations, churches, businesses, and other groups in the community also pitched in to assist with registration, event and course setup/teardown and handling of numerous other race details before and during the event. For the fourth consecutive year, Allan Cason from APC Entertainment served as DJ and master of ceremonies. He sang incredible renditions of “The Star-Spangled Banner” and “God Bless the USA (aka “Proud to be an American”) to start off the 10k and 5k races, respectively, which got our racers in the spirit of the occasion and ready to run!

The Research for Cure 501(c )3) charity was created by Fran Lopes in 2002, and to date has raised over $900,000 from Plymouth Rock ‘n’ Run, golf tournaments and other fundraising events to benefit RIRC. The PRNR team has already starting planning its 2017 Thanksgiving Day turkey trot, marking its 10-year anniversary. Come join us for a morning filled with fun and healthy activity in support of the Reeve-Irvine Research Center! You can organize your own fundraising team with your family and friends and help to make the race proceeds even more successful. Or just show up in costume and be in the pool of folks who may win a prize for best costume! If you cannot make it to the race please consider taking part in the virtual run, join a team on line or help with sponsorship. There are so many ways to support this amazing group in their efforts to make a difference in the lives of those who need to believe in a better tomorrow. For more information about the race and sponsorship opportunities, please visit the Plymouth Rock ‘n’ Run website at www.plymouthrocknrun.com or contact Tania Jope at (949) 824-5925 tania.jope@uci.edu.
Don’t Miss this Event!

The 2017
Meet the Scientists Forum

Saturday, March 11, 2017
12 pm
William J. Gillespie Neuroscience Research Facility

~ Hear the latest research updates
~ Interact with Researchers
~ Participate in lab demonstrations

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 GHRF
Irvine, CA 92690-4292

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

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Moonlight over the RIRC

Photo by Os Steward
IRA Rollover Gifts

Charitable IRA Giving
Congress recently changed the rules for charitable gifts made from IRA’s. If you are over age 70 1/2, the Federal government now permits you to rollover up to $100,000 from your IRA to charity without tax.

To learn more about IRA Rollover Gifts, call Roland Ho at 949.824.6454 or visit our website at

www.ucifuture.com

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NOW ENROLLING!

Do you have hand or arm impairment after a stroke or 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”

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

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