Number 31, Fall 2018

Reeve-Irvine Research Center Publication

Spinal Connections

Update on clinical trials for spinal cord injury

Data continues to come in on the results of clinical trials involving stem cells for spinal cord injury.

The SCiStar study

The company Asterias has completed enrollment and dosing in all 5 of its planned SCiStar study cohorts. This is a Phase 1/2a clinical trial to evaluate safety and potential efficacy for severe cervical spinal cord injury. Readers of Spinal Connections know that the foundation for the Asterias trial was the paper in 2005 by Hans Keirstead at the RIRC (Keirstead, H.S., Bernal, G., Nistor, G., Totoiu, M., Cloutier, F., Sharp, K., and Steward O. Human stem cell derivatives remyelinate and restore locomotion after spinal injury. J. Neurosci., 25, 4694-4705). The clinical trial for oligodendrocyte precursor cells (OPCs) was initially launched by the company Geron and was the first ever trial for human stem cells for spinal cord injury. This trial was terminated for economic reasons and the company Geron folded but the company Asterias re-booted the trial with their product called "AST-OPC1".

Dr. Oswald Steward

On July 31, 2018 Asterias reported 12 month data for cohort 3 and 4 updating previous reports on the data from earlier time points. Those of you who have been following this know that there are 5 cohorts in the trial. Cohort 3 involves 6 subjects with cervical level injuries who are motor complete (AIS-A) who received 20 million cells. Cohort 4 involves 6 subjects with cervical level injuries who are AIS-B who received 20 million cells.

Overall, there continues to be a positive safety profile with no serious adverse effects related to the transplanted cells. Magnetic resonance imaging (MRI) studies at 12 months are consistent with the formation of a tissue matrix at the injury site in 92% (11/12) subjects, suggesting reduction in cavity formation. At 12 months 100% (6/6) subjects in cohort 3 have recovered at least one motor level on at least one side and one subject recovered two motor levels on one side. For the combined data for Cohorts 2-4, 94% (17/18) subjects recovered at least one motor level on at least one side. Asterias expects to publish 12 month data for the entire study in the first quarter of 2019.

On October 31, 2018, Asterias announced that an independent Data Review Panel recommended moving forward with the clinical development of OPC1. The next step is a meeting with the Food and Drug Administration (FDA) to discuss the path to development and trial design for a controlled Phase 2 clinical trial that could begin in 2020.

Data from the Phase 1/2a clinical trial continues to be promising, but there is a looming hurdle for Asterias in terms of funding to go forward. The larger Phase 2 controlled efficacy trial will cost tens of millions of dollars.

In August, a thoughtful article on the Asterias trial and some of the participants was published in the San Francisco Chronicle by reporter Erin Allday:
https://projects.sfchronicle.com/2018/stem-cells/research/

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Continued from Cover

First-in-Human, Phase I Study of Neural Stem Cell Transplantation for Chronic Spinal Cord Injury:

In June, a peer-reviewed paper was published on the outcome of a Phase I trial involving human spinal cord-derived neural stem cells (NSCs) that are the commercial product of the company Neuralstem Inc. (Curtis et al., 2018, Cell Stem Cell 22, 941-950). NSC's differ from embryonic stem cell-derived oligodendrocyte precursor cells (OPCs) because the NSCs have not yet become committed to a particular cell type and thus can differentiate into all three of the primary types of cells in the central nervous system (neurons, oligodendrocytes and astrocytes).

The NSC product (NSI-566) was derived from a single post-mortem spinal cord from an 8-week gestational age human fetus. Cells were dissociated from the spinal cord and a single line of cells was expanded under good manufacturing practice (GMP) guidelines to generate a cell bank for clinical use. These cells had previously been tested in a clinical trial for ALS.

Subjects for the trial were individuals with chronic spinal cord injuries, defined as at least one year but no more than 2 years after traumatic SCI. The trial involved four subjects classified as AISA-A, a motor and sensory complete SCI, levels T2-T12 who received injections of NSC into the spinal cord. Each subject received a total of 6 injections of 2 million cells/injection. Injections were placed bilaterally into the remaining tissue lateral to the injury site and within white matter approximately one segment below the injury site. Data are from subjects who were followed for 18-27 months.

All subjects tolerated the procedure well and there were no serious adverse events. Three subjects exhibited one to two levels of neurological improvement in motor and sensory scores, which is considered to be an early sign of potential efficacy. However, there was no improvement in quality of life scores.

Despite these encouraging data, the authors emphasized that this study was designed as a safety trial without statistical power or a control group needed to evaluate any functional change resulting from cell grafting. Nevertheless, the favorable safety profile and hints of potential efficacy could warrant follow-up dose-escalation studies. Also, the study provided additional data supporting the feasibility of the approach of injecting cells into the injured spinal cord.

Perspective on progress:

It's important to emphasize that it is really a mark of progress that these clinical trials have been carried out. When we launched the RIRC in 1999, there were NO ongoing clinical trials for people living with SCI, and the question was always "when will there be clinical trials"?

At the same time, we need to keep in mind that the treatments being tested today are really first generation. If this was a computer application, you could think of this as version 1.0. The original science documented measurable but modest improvements in motor function in rodents, and the functional gains in people have so far been modest. Building upon these positive beginnings, we can move on to discover better and more effective therapies (version 1.1, 1.2, etc.).

Everything being done today to test new therapies in studies costing millions of dollars began as a new idea for which a small amount of money was needed to get the initial preliminary data. To get version 1.1, 1.2 etc. therapies, we need to be able to generate preliminary data to test these new ideas in order to be able to get further funding to develop them. Private donations for the first stage of innovation are the seed from which the gigantic tree grows.

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In this issue...

Dr. Marion Murray

We are sad to report that Dr. Marion Murray, one of the most accomplished and highly respected leaders in spinal cord injury research, passed away on September 9 following complications of esophageal cancer.

At the time of her death, Marion was professor emeritus in the Department of Neurobiology and Anatomy at Drexel University. Marion was a founding member of the Spinal Cord Research Center at Drexel University, leading its research activities for over 30 years to create one of the most prominent centers in the United States.

The focus of Marion's research was on neuroplasticity and its relation to recovery of function after spinal cord injury. Her early studies with her collaborator Dr. Michal Goldberger were amongst the first to report evidence that sprouting of novel connections after spinal cord injury led to the formation of functional connections. This was at a time when almost everyone in our field believed that the mature nervous system was completely incapable of any growth after injury. Her work helped to fundamentally change our understanding of how the nervous system responded to injury, leading to our current understanding that the limited growth that does occur is part of the mechanism underlying naturally-occurring recovery of function. This concept was a sea change that gave new hope -- if we could understand the mechanisms of sprouting, we might be able to harness those mechanisms to enable robust regeneration of connections in the injured spinal cord. Following from those groundbreaking studies, Marion went on to make major contributions to our understanding of the role of axonal regeneration and sprouting in functional restoration after injury and on mechanisms of neuroprotection.

Marion exemplified a scientific leader who passionately confronted significant problems for human health and then generously shared her knowledge with others. Under her leadership, the Spinal Cord Research Center at Drexel established multidisciplinary research training in spinal cord injury and created a program that continues to have international impact, with influence in basic and translational neuroscience beyond her initial vision.

Dr. Murray received her PhD from the University of Wisconsin in physiology and did her postdoctoral work 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 in 1973 moved to the Medical College of Pennsylvania, which was the predecessor of Drexel University.

Dr. Murray received numerous awards, including the NIH Javits Neurosciences Investigator Award, the Fogarty Fellowship, the MCPHU Research Achievement Award and, most recently, the Reeve-Irvine Research Award. She served on the editorial boards of scientific journals such as Experimental Neurology and Journal of Comparative Neurology; on scientific review committees, including for the NIH and the VA; and as the scientific director of the Craig H. Neilsen Foundation.

In recognition of her lifetime of achievements and contributions, the Drexel University Center for Spinal Cord Research will be dedicated and named in the memory of Marion Murray.

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Are you considering including Reeve-Irvine in your estate plans?
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For information please contact:
Krista Barajas, Reeve-Irvine Administrator
(949) 824-0210 or email k.barajas@uci.edu

Anatomy 101

Gene Targeting to enable regeneration after Spinal Cord Injury

Mariajose Metcalfe and Os Steward

It's well accepted by scientists that the best hope for functional recovery following spinal cord injury is to regenerate the connections that were damaged. It's also well accepted that there are 2 major reasons that regeneration doesn't occur: 1) Adult neurons have very limited "intrinsic capacity" for growth; 2) The lesion site is a hostile environment for growing nerve connections (axons) with chemical and physical impediments that block growth, many of which are expressed by inflammatory cells and glial cells (astrocytes). Over the past decade, researchers have begun to see some real successes with approaches that target genes to enhance intrinsic growth capacity and modify some of the chemical barriers at the lesion scar.

What do we mean by "gene targeting". This isn't an intervention to alter a person's genes (DNA sequence) as might be done to correct a defective gene. Instead, scientists are using new approaches that target the molecules that carry information from the gene in DNA to the cytoplasm of the cell where proteins are made called "messenger RNA", abbreviated "mRNA". Remember the "central dogma" of molecular biology, genes are DNA, DNA encodes for mRNA, mRNA encodes for different proteins. So, if you have a protein (gene product) that is doing something you don't want, target the mRNA that makes the protein.

In the context of SCI, the idea is to deplete (knock down) proteins that halt regeneration. For example, O. Steward's work follows up on the discovery that intrinsic growth capacity of adult neurons is shut down by proteins that are expressed as neurons mature (growth suppressors like the molecule PTEN). Intrinsic growth capacity is what enables neuron growth during development. So, to enable regeneration of the corticospinal tract, which controls our ability to move voluntarily, the strategy is to knock down PTEN. Similar approaches are being used to knock down molecules that inhibit growth at the lesion site, like the inhibitory molecule chondroitin sulphate proteoglycan, which is expressed by astrocytes at the lesion scar.

Viral-mediated delivery routes for therapeutic genes.

So, how do we target mRNA in cells like neurons to knock down expression? There are two parts to the story; the first is to harness viruses as delivery vehicles; the second is to engineer the viruses to express what might be called "anti-mRNAs".

Viruses are very simple organisms that have a protein coat (called a "capsid") surrounding genetic material (genome) which is in the form of a circle. Viruses work by binding to cells and injecting their genetic material into the "host" cell. The viral genes take over the machinery of the host cell so that the host starts making viral proteins, which cause disease, often by killing the infected cell.

Scientists have been able to take advantage of the ability of viruses to bind to host cells and inject their DNA. The trick is to engineer the viral genome, removing harmful genes and genes that enable viral replication and inserting genes that do something else (in our case, synthesize an "anti-RNA"). The result is a "viral vector" that is a therapeutic candidate.

Anti-RNAs are short RNA molecules that have a sequence that is "complimentary" to a short stretch of the target mRNA. Depending on their physical form, these "anti-RNAs" are called short hairpin RNA (shRNA) or short interfering RNA (siRNA). When these anti-RNAs bind to the target mRNA, this causes the cell to mount a response that rapidly degrades (knocks down) the target mRNA. As a result, the targeted protein is not synthesized.

Using AAV to knock down PTEN expression.

This is the scientific background for the candidate therapy being developed by Steward's research group at RIRC. The approach was initially developed by Dr. Gail Lewandowski in Steward's research team and uses an AAV vector that targets neurons.

The AAV vector expresses shRNA against PTEN, so when the AAV/shPTEN is injected into the motor cortex, the vector is taken up by the cells of origin of the CST, and PTEN expression is knocked down. This activates a growth program in adult CST neurons that enables regeneration.

Our published studies have shown that decreasing PTEN promotes unprecedented regeneration of the injured tracts and improves motor function of the upper extremities. So far, we haven't seen any treatment-related adverse events, but one potential issue for translation is that we used an AAV virus that once it is injected, it is always "on" meaning that it will continue to knock down PTEN even after regeneration has been achieved. A desirable characteristic for a therapeutic candidate is to be able to regulate expression of the shRNA in a defined time frame after the injury. For this, Steward's research team is now testing AAVs with an "on-switch".

AAVs with regulated expression

A huge advance in AAV vector biology has been the development of new AAV vectors that allow "regulated expression". Synthesis of the AAV cargo (in our case shRNA) can be turned on by giving a drug that is actually already approved for human use (the antibiotic tetracycline or doxycycline). What is exciting about this approach is that we can precisely control how long the therapy is delivered by using the 'on-switch', and turn off the AAV by discontinuing the drug when regeneration and recovery are complete.

Steward's research team is launching studies to test out this new approach, which will be an important step toward developing the final "therapeutic candidate" to advance to the FDA as an investigational new drug (IND). There are already several ongoing trials involving AAV-based therapies and just this year, a clinical trial of an AAV-based therapy for the treatment of spinal muscular atrophy (SMA) reported remarkable efficacy. These are exciting times for sure in terms of developing new therapies for SCI.

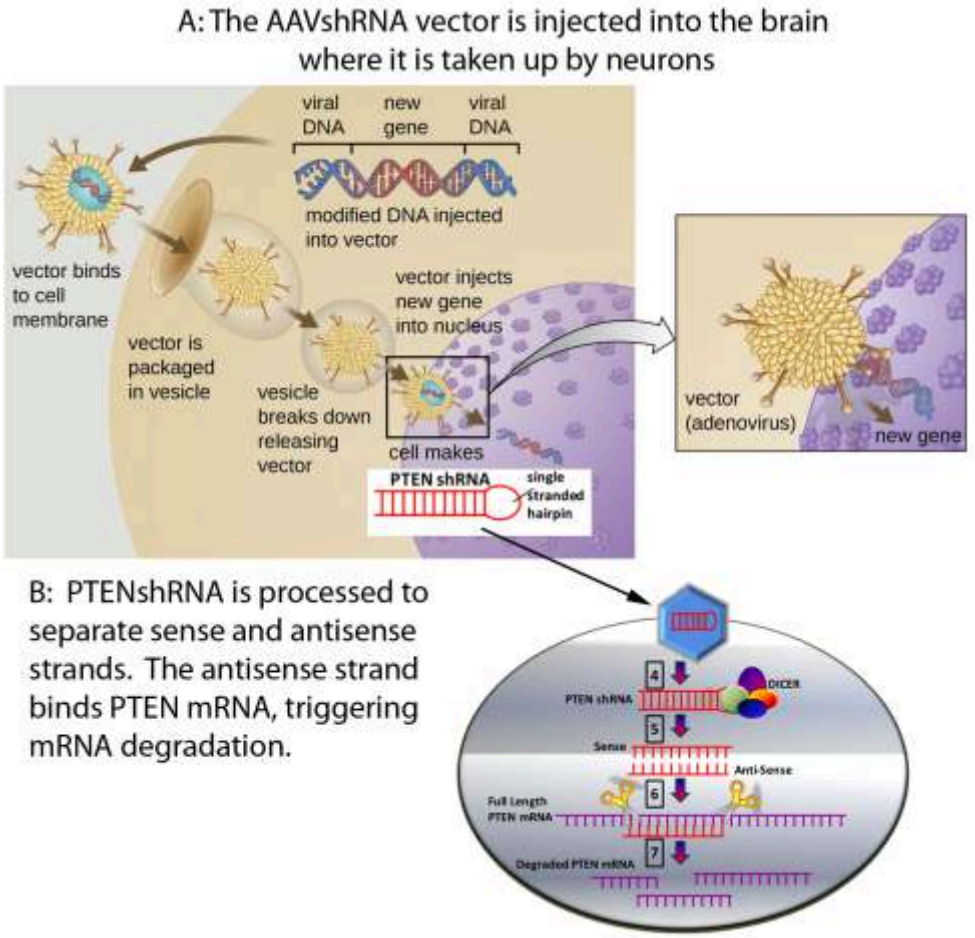


Figure 1. AAV vector expressing shRNA against PTEN triggers degradation of PTEN mRNA. Our AAV vector expresses shRNA against PTEN and a fluorescent reporter ZsGreen. When the AAV/shPTEN vector is injected into the brain, it binds to particular types of neurons and is taken up. Neurons express shRNA from the AAV DNA, which is processed to generate a short sequence that binds to PTEN mRNA, triggering degradation of the PTEN mRNA.

Image credits: A:Modified from https://courses.lumenlearning.com/microbiology/chapter/gene-therapy/
which is a modified figure from NIH.

B: From Gail Lewandowski

RIRC 2018 Summer Research Team

Each summer, RIRC hosts undergraduate students and summer interns who are interested in gaining experience in working in a lab. The 2018 summer Research Team was spectacular and included:

Bridges to the baccalaureate program

Hana Abdirahman participated in the Bridges Program to prepare to transfer to UCLA in Fall 2018 as a Neuroscience major. Hana is a first-generation college student from Somalia. She was born in the Middle East and her family migrated to the United States for a better future. She spent the first two years of college at MiraCosta College where she developed a particular interest in organic chemistry and biology. She says: "After I complete my undergraduate degree in Neuroscience, I plan on continuing my education by pursuing a doctorate degree in the same field. My long-term career plan is to become a researcher/professor in the neuroscience field. Neuroscience is a large field that encompasses many disciplines, but I am chiefly interested in the molecular and cellular mechanisms that are yet to be understood. In my free time I like to catch up on popular television shows, hang out with my sister and go to my favorite place in all of Southern California, the Los Angeles County Museum of Arts".

Christy George participated in the Bridges Program to prepare to transfer to a research university for the 2018-2019 academic year. Christy is 19 years old and Egyptian-American. She graduated from high school at 16 and currently attends Cerritos College as a Biology major where she earned both her Associates in Arts in Biology and Natural Sciences at age 17. Christy plans to continue her project in Os Steward's lab on PTEN knockdown as a means to slow neurodegeneration in a mouse model of Alzheimer's Disease. She says: "It is a dream come true to be able to work in AD research, as I had previously been in a club dedicated to raising money for a cure, and now I am in the lab and studying the disease first hand. In addition to research, I enjoy spending time sewing clothing, volunteering at my local hospital, and going to church. This summer has given me the opportunity to truly fall in love with the field of neuroscience and the ability to learn about what has never been seen before. I am so excited to continue my work in the lab and grow as a future neuroscientist!"

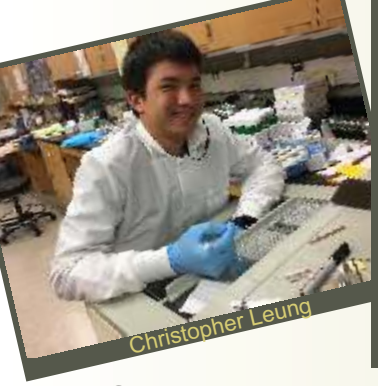
Daniela Gonzalez participated in the Bridges Program to prepare to transfer to UCI. She began her undergraduate education at Fullerton College where her passion for science was sparked by Dr. Mary Nolan-Riegle. She says: "As a first-generation Latina, going into the STEM field was only a dream, but with Dr. Nolan's mentoring and support I made my dreams my goals". At Fullerton College, Daniela was as a General Biology tutor and conducted biochemical research with the RAISE 2017 program at Cal State Fullerton with Dr. Maria Linder. Her future plans are to continue to learn about the nervous system and innovate the physical therapy field with noninvasive techniques. "I want to focus on sports injuries and spinal cord injuries. My goal is to continue to stay humble and open minded in hopes of connecting with scientist of all generations so we can all collectively be our best".

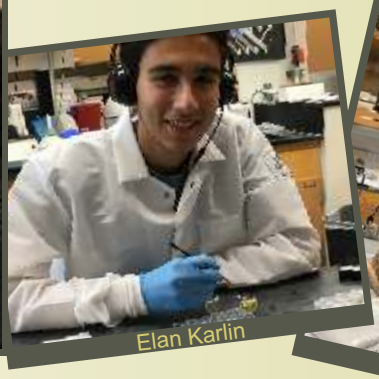
In addition to students in the "Bridges" program, we were fortunate to have several other very talented and dedicated summer interns (research volunteers). Most are undergraduate students at other universities who are Orange County residents and are home for the summer. Others are highly motivated high school students.


Hana Abdirahman


Christy George


Daniela Gonzalez


Christopher Leung


Elan Karlin


Megan McCune

Summer research interns

Megan Barajas is starting her senior year at Pacific Ridge High School. She says: "I chose to spend my summer working in the lab because I thought this would be a great opportunity for me, as decisions about colleges are coming soon, to explore different options and career paths I could take down the road. Working in the lab has been a really great learning experience for me and I am so happy and thankful that I have been able to be a part of this respectful and helpful work environment."

Elan Karlin is starting his junior year at UCLA majoring in Molecular Cellular Developmental Biology. His home is in Orange County. Elan had previous experience working in labs including NAMSA Medical Research Organization and with an orthopedic surgeon at UCLA. He says, "Working in this lab was an enriching experience and peaked my interest in neuroscience. I gained a deeper understanding of the connections within the nervous system and the damage that spinal cord injuries may inflict. While working, I was able to gain skills in lab bench work and critical thinking that will undoubtedly translate to my research at UCLA and one day in the medical field. I am grateful for the opportunity to have worked in this lab and hopeful that I will be able to continue working in research."

Christopher Leung is a rising senior at Valencia High School, in the city of Placentia, California. At Valencia, he is involved in the International Baccalaureate and Valencia Technology programs, the latter of which involves the completion of a 150-hour internship for the purpose of acquiring work experience and gaining exposure to potential career pathways. He says: "I have a strong desire to pursue a college major and career in the sciences, and consequently I sought to find an internship that would align with these aspirations. When I found out about this opportunity, I immediately emailed Kelly Yee with my resume and an expression of my interest in working in a laboratory environment. Although it was somewhat intimidating at first to be working in such an environment alongside individuals who are older than me, I am very happy that I have been provided such an opportunity and I realize that I am very fortunate to be able to gain real-world work experience through performing actual research at the university level. My participation in the lab as an intern this summer has provided me with new insight about this field, in addition to reaffirming my interest in pursuing a major within this discipline as I continue to progress in my studies at an institution of higher education".

Megan McCune is an Orange County resident who is a biology major at Providence College. She will be entering her senior year this fall. She says: "My mom works as physical therapist for children with a variety of movement disorders and injuries and through this experience I became very interested in motor neuroscience. I plan to pursue graduate research after Providence and am very grateful for the opportunity to learn so much about spinal cord injury research through volunteering this summer in the Steward Lab".

Grace Axelson is starting her junior year at UC Berkeley as an Integrative Biology major on the Human and Health Sciences track, with a minor in disability studies. She ultimately hopes to attend medical school and pursue a career in medicine. She says: "I am so thrilled to have spent my summer working in the lab. Due to my commitment and passion for science, I wanted to work in the lab over the summer in attempt to see every part of science that I can, and expose myself to new aspects of biology that my classes at Berkeley have not yet shown me. Outside of academics, my interests are dance, fitness, travel, and spending time with friends and family."

Rafae Pasha is a sophomore at UC Berkeley. He plans to study both chemistry and neurobiology and hopes to eventually go into the medical field. He says: "I chose to spend my summer in the lab because I felt that it would provide me with valuable experience in a lab setting as well as getting to work on some really cool projects! My interests include producing music, playing video games, and cooking."

Devoted Service Appreciated

Tania Jope

It is with very mixed emotions that we said au revoir and happy retirement to Tania Jope earlier this year. As all regular readers of the RIRC newsletter know, Tania moved with Os from the University of Virginia to help found the RIRC in 1999. She began as the Chief Administrator of the RIRC, but quickly took on the more critical role of Director of Community Development, coordinating all of the fundraising activities of the RIRC. It was in this role that so many of you came to know and appreciate Tania. Tania and her husband Nick and their two children Ryan and Sophia moved to Phoenix in July to start the next chapter in their lives, in part to take advantage of very unique school opportunities for the kids. We will all truly miss Tania's commitment and hard work to fulfill RIRC's vision of a better world for people living with spinal cord injury.

We are fortunate that Krista Barajas who currently serves as Chief Administrator for the RIRC will take over Tania's responsibilities as the principal contact for donations and volunteer support for the RIRC. Krista's contact information is: Krista Barajas – e-mail: k.barajas@uci.edu – phone: 949-824-0210

Karla Banos McHale

With mixed emotions, RIRC bids adieu to Karla Banos McHale. Karla and her husband, Dr. Peter Thomas McHale, and family have moved to the University of Utah, where Peter has been appointed as Senior Analyst/Programmer in the Department of Human Genetics.

Karla was one of the first employees when RIRC was founded in 1999. Karla received her undergraduate degree at UCI in 1999, and before Os even arrived, wrote him and asked to work in the lab. This was a long-standing goal: she wrote in her high school yearbook that she wanted to do research on spinal cord injury.

Karla helped launch the research in the RIRC, initially working with Denise Inman, who had moved with Os to UCI and was completing her dissertation for a PhD in Neuroscience from UVA. Karla initially assisted with tissue dissection and histology, and then with spinal cord injury surgeries.

Karla continued at RIRC for several years, but then took a position at Cal. State University LA where she worked with Ray DeLeon on spinal cord surgeries in young rats. Then, in 2008, she took a position at UCSD with Mark Tuszynski and Paul Lu, where she learned embryonic surgery to isolate tissue to prepare neural stem cells. While at UCSD, Karla met and married her husband.

Peter accepted a postdoctoral fellowship at UCI in 2009 in the Department of Cell and Developmental Biology in the Center of Complex Biological Systems. Karla had full time responsibilities as a mom with 3 children, but returned to RIRC part time to work evenings and weekends. From 2015-2018, Karla continued to make major contributions to the research activity of the center.

Best of luck Karla and family!

Shannon Farris

Former Reeve-Irvine graduate student Shannon Farris is appointed Assistant Professor at Virginia Tech Carilion Research Institute. Shannon completed her graduate training in 2012 under the mentorship of Dr. Os Steward. Following her graduate training at UCI, Shannon was appointed Postdoctoral Fellow at the National Institute of Environmental Health Sciences, NIH.

Congratulations Shannon on your new faculty position at Virginia Tech Carilion!

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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Spinal Connections is a publication of
Reeve-Irvine Research Center
University of California, Irvine
1105 Gillespie Neuroscience Research Facility
Irvine, CA 92697-4265
949-824-0210
www.reeve.icu.edu

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MEET THE SCIENTISTS FORUM

The California Spinal Cord Injury "Meet the Scientists" forum brings together scientists, researchers, clinicians, associates and students to give individuals an opportunity to meet, ask questions, and hear about the latest advances in spinal cord injury research.




This year's event will be held on Saturday, March 16th, 2019 12:00pm – 2:30pm.
Gillespie Neuroscience Research Facility, 837 Health Sciences Road, Irvine, CA 92697-4265

Hot Topic - - - Epidural Stimulation

Epidural Stimulation enables some voluntary movement

By Mariajose Metcalfe Ph.D

Epidural Electrical Stimulation (EES) is the application of electrical pulses to the lower part of the spinal cord below an injury. The stimulation is generated via a small chip that is implanted over the protective coating (dura mater) of the spinal cord. A remote control about the size of a smart phone controls the frequency and intensity of the electrical current. Although research on this approach has been ongoing for some time, this year was special because of new reports that some people who were previously thought to be completely paralyzed are able to voluntarily move their legs when the stimulator is on, and other subjects with some residual motor function but couldn't walk, became able to walk over-ground with assistive devices.

These breakthrough reports are from long-term studies led by different Principal Investigators, two of whom are previous recipients of the Reeve-Irvine Research Medal (Reggie Edgerton at UCLA and Susan Harkema at the University of Louisville, Kentucky).

In a study published in 2018 in the prestigious New England Journal of Medicine, Dr. Susan (Suzy) Harkema and her group at the University of Louisville report enhanced brain-to-spinal cord connectivity in subjects with complete paralysis. Here, they tested effects of EES combined with intensive locomotor treadmill training with weight support in 4 patients 2.5 to 3.3 years after SCI. Two of the four research participants developed the ability to walk over ground with a walker with no assistance from a therapist. In addition, all four participants achieved independent standing and improved trunk stability while maintaining their mental focus, which is defined as purposefully wanting to pick up their foot or leg to take steps.

Although improved motor function is only seen when the stimulator is on, there were other positive benefits that persisted, including improved function of the autonomic nervous system (temperature regulation, enhancement in sexual function, increase in bladder control and overall improvement in sense of quality of life).

In the new study, the subject received additional "multi-modal rehabilitation (MMR)" for 43 weeks. Eventually, the subject recovered the ability to walk over ground while using a front-wheeled walker with trainers providing only sporadic assistance.

Then, another study came out in September 2018 in the prestigious journal Nature Medicine from Reggie Edgerton's group at UCLA along with researchers from the Mayo Clinic. This paper reported new findings involving a subject with complete loss of function below the sixth thoracic spinal segment due to SCI that occurred 3 years prior to study enrolment. The subject previously had 22 weeks of locomotor training before the implantation of the EES system. After the implantation of the EES device and training, the subject was able to stand and generate step-like leg movements when the EES was on. In the new study, the subject received additional "multi-modal rehabilitation (MMR)" for 43 weeks. In the MMR training sessions, the subject first worked on voluntarily moving the legs with the EES turned on and then on standing and stepping with trainer assistance and body-weight support as needed. Eventually, the subject recovered the ability to walk over ground while using a front-wheeled walker with trainers providing only sporadic assistance. Additionally, he was able to take bilateral steps on a treadmill.

Is EES alone enough to regain locomotion? The short answer is no. All the studies published have shown that pairing implantation of the EES chip with locomotor training is needed for the success of the treatment. The stimulator may excite the spinal cord, but rehabilitative training is required to achieve recovery.

How to Help - Turning SCI into Advocacy

By Mariajose Metcalfe

Ph.DEric LeGrand is a former football defensive tackle that played college football at Rutgers University. Eric suffered a career ending cervical spinal cord injury while making a tackle in an October 2010 game.

Eric is now tetraplegic, but this hasn't slow him down. A few months after his injury, he resumed his college classes via Skype and also launched his sports broadcasting career as an analyst for Rutgers Football Radio Network. Eric has also become a much sought after motivational speaker.

The whole nation was a witness of Eric's accident, leading to an outpouring of support. Humbled by this outpouring of support, Eric decided to form a charity, "Team LeGrand", whose proceeds go toward research to find a cure for paralysis and helping improve the quality of life for people with spinal cord injuries.

Last year Eric hosted "An Evening with Eric LeGrand", which raised more than $1 million for spinal cord injury research. This year Eric will again host "An Evening with Eric LeGrand" and also the "Eric LeGrand Flag Football Tournament" and "A Walk to Believe" where he hopes to raise $2 million. ""Each year, it's been amazing," LeGrand said. "We just want to get to our goal of $2 million raised. Last year, these events put us over $1 million, so now we're working and grinding away to get to $2 million."

"I believe Christopher Reeve started something, and I'm supposed to finish it. While I've been so fortunate in my recovery process, there are so many people living with spinal cord injuries who don't have access to the proper resources", says LeGrand. "By creating Team LeGrand, I'll be able to help all of those individuals on their road to recovery, and together we can achieve Christopher Reeve's dream of empty wheelchairs."

If Eric LeGrand's story inspired you, there are many things that you can do to help raise funds for spinal cord injury research to help create tomorrow's cures. For more information please contact Krista Barajas at k.barajas@uci.edu

Continued from facing page

This research is based on two distinct treatments: epidural stimulation of the spinal cord and locomotor training. Epidural stimulation is the application of electrical pulses at varying frequencies and intensities to specific locations on the lumbosacral spinal cord. This area of the spinal cord, controls movement of the hip, knees, ankles and toes. The locomotor training aims to retrain the spinal cord to achieve the pattern of walking by repetitively practicing standing and stepping. Combining both treatments will play a critical role in enabling stepping abilities.

Although this is very exciting, things are still at an early stage, and there are some limits and caveats. First, improved function requires many weeks of intense rehabilitative training paired with EES. Second, not all SCI subjects will benefit from the approach. For there to be any voluntary motor function, subjects must have some spared connections across the injury. In this regard, an important scientific discovery is that some subjects that were diagnosed as having no spared functional connections (termed "motor complete") were nevertheless able to move with stimulation. Going forward, it will be important to find a way to identify which subjects can benefit before asking the subject to invest all the time required for training.

Epidural stimulation has transformed our understanding of "complete" injuries and suggests that even people previously diagnosed as motor complete may no longer face a lifelong sentence of paralysis. Spinal neuromodulation in the presence of a task-specific training can enable functions that were once thought to be permanently lost following SCI. Right now more clinical research must be done with larger cohorts in order to translate the treatment to a larger population of SCI community.

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R|RC Reeve-Irvine Research Center

MEET THE SCIENTISTS EVENT

Saturday, March 16, 2019
12:00–2:30 pm

University of California, Irvine
Gillespie Neuroscience Research Facility
837 Health Sciences Road, Irvine

For more information go to www.reeve.uci.edu
or email k.barajas@uci.edu

10th Annual

Plymouth Rock'n' Run

5k/10k run/walk // 1k kids run

THANK YOU

Plymouth Rock 'n' Run and Research for Cure for hosting and organizing another great trot on Thanksgiving Day!

Come trot with us next year!

Thanksgiving morning // 11.28.19
yorba regional park //anaheim hills

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Plymouth Rock 'n' Run is brought to you by ResearchforCure, a501(c)(3) charity supporting spinal cord injury research at the Reeve-Irvine Research Center (RIRC), UC Irvine

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