

Spinal Connections

Reeve-Irvine Research Center Publication

Zhigang He Awarded Reeve-Irvine Research Medal



Zhigang He, Ph.D.

We're delighted to announce that Dr. Zhigang He is the recipient of the 20th Reeve-Irvine Research Medal. This award is to recognize Dr. He's fundamental contributions to our understanding of why injured axons don't regenerate in the adult mammalian central nervous system (CNS), and how their regeneration can be enabled by targeting the intrinsic growth capacity of adult neurons.

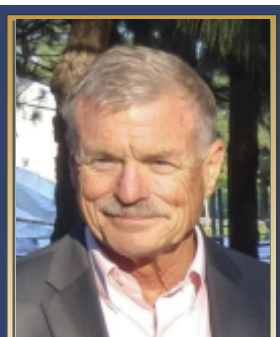
The Reeve-Irvine Research Medal was established in 1996 by Joan Irvine Smith, and is continued through the generosity of the Joan Irvine Smith and Athalie R. Clarke Foundation. The award was originally named "Christopher Reeve Research Medal", but with Christopher's blessing,

became the "Reeve-Irvine Research Medal" when the RIRC was founded.

The Medal, which includes a \$50,000 cash award, 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. This ongoing award enables us to continue to recognize the work of pioneering investigators whose research brought us closer to cures for afflictions affecting the spinal cord.

Dr. He received his Ph.D. from the University of Toronto and was a postdoctoral fellow with Dr. Marc Tessier-Lavigne at the University of California, San Francisco. Dr. Tessier-Lavigne was co-recipient of the 11th Reeve-Irvine Research Medal with Dr. Corey Goodman. Dr. He has the honor of being named a Klingenstein Fellow in Neuroscience and John Merck Scholar and McKnight Scholar. He is the director of the Boston Children's Hospital Viral Core, which aims to provide technological resources to academic investigators interested in the development and use of viral based vectors. Dr. He has published over 190 articles and his research is supported by the NIH and several foundations.

A lot of things have been going on at RIRC over the past few months, mostly good but some not so good and the not so good has been occupying a lot of our time during the early fall.



Dr. Oswald Steward

To get the not so good out of the way first, on September 21 our building (the Gillespie Neuroscience Research Facility) experienced a disastrous flood. This was the result of a burst cold water pipe that goes into the air conditioning units on the roof. The pipe is the size of a fire hose, and water sprayed out at a rate of hundreds of gallons a minute, coming down throughout the building. For those of you who have visited our center, imagine a waterfall coming down from the 3-story high ceiling in the foyer. Fortunately, this happened during the day (although on a weekend) and people were working in the lab and quickly reported the flood. Still, it took time to shut the water off, and so our building experienced major damage, mostly in the form of soaking sheet rock and wood trim. Fortunately, graduate student Jen Yonan was working in our labs and was able to cover sensitive equipment so damage was minimal. Even more fortunately, the hundreds of mice and rats we have in our colony were OK.

The building was completely closed for several days to assess whether it was safe to return due to water in electrical systems. The university contracted with a disaster response team who immediately began the job of repairing the damage, and they have been wonderful in cooperating with us so that we were able to continue to do critical research in the lab. As of mid-November, we have been able to return to our offices after replacing sheet rock and carpet, and repair work in the labs is nearly complete although a lot still needs to be done on the upper floors of the building, which suffered even more severe damage than we did. It has been a mess to say the least, but operations are recovering and we hope to have things back mostly to normal by the first of the year.

Now on to the good things:

- 1 - Our research programs have been going extraordinarily well!
- 2 - New faculty have joined the RIRC and one of our former senior investigators has returned to UCI (Tom Lane);
- 3 - New research programs have been launched (see Anatomy 101);
- 4 - New NIH grants have been awarded, documenting the cutting edge nature of our research programs;
- 5 - We hosted a spectacular symposium/workshop honoring Dr. Zhigang He as the 20th recipient of the Reeve-Irvine Research Medal.

More on all these things in Articles throughout our fall newsletter.



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Viral vectors for gene modifications to enable regeneration after spinal cord injury

On November 8th, the RIRC hosted the Reeve-Irvine Research Medal Symposium titled “Viral vectors for gene modifications to enable regeneration after spinal cord injury”. The symposium brought together scientists who are leading efforts to harness viral vectors to enable regeneration or improve functional outcome after spinal cord injury. We called the event a “workshop” because it was designed to foster exchanges of information and promote new collaborations, which it definitely did!

Distinguished Speakers



Zhigang He, Ph.D.

Professor of Neurology
Boston Children’s Hospital
F.M. Kirby Neurobiology Center

From axon regrowth to functional restoration after spinal cord injury.



Kevin Park, Ph.D.

Associate Professor
Department of Neurological Surgery
University of Miami School of Medicine

Cell-type specific axon regeneration and target selection promoted by gene modulation.



Murray Blackmore, Ph.D.

Associate Professor
Department of Biomedical Sciences
Marquette University

Transcription Factor Synergy for Axon Growth: Detection and Deployment.



Binhai Zheng, Ph.D.

Professor, Department of Neurosciences
Director, Microscopy Imaging Core
University of California, San Diego

Investigating the multicellular response to injury in the mouse spinal cord.



Veronica Tom, Ph.D.

Associate Professor
Department of Neurobiology and Anatomy
Drexel University

Attacking from multiple angles: tackling extrinsic and intrinsic barriers to functional axonal regeneration after injury.



Mark Tuszynski, M.D., Ph.D.

Professor, Department of Neurosciences
Director, Center for Neural Repair
University of California, San Diego

Gene delivery in rodent and primate models of spinal cord injury.



Os Steward, Ph.D.

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

Harnessing retro-AAVs for gene modifications to enable regeneration after spinal cord injury.

Katie Thompson-Peer highlighted by The Scientist as one-of-ten rising stars in neuroscience



Nervous systems are comprised of individual nerve cells, AKA neurons, that communicate with each other in circuits. Neurons have an architecture that resembles a tree: they have a highly branched arbor and a single long trunk that splits into roots. The branches of the arbor are called dendrites, and the single long trunk is the axon. Dendrites act as the antennae for the neuron: they allow it to receive information. The axon allows the nerve cell to send signals to other neuron or muscle cells that may be far away. Input through the dendrite arbor antennae, output through the axon to the target cells.

When Dr. Katherine Thompson-Peer, PhD, a new fellow of the RIRC, began her work as a postdoctoral fellow with Dr. Yuh-Nung Jan, PhD, at UCSF and the Howard Hughes Medical Institute, she realized that although scientists have considerable insights into when neurons can or cannot regenerate axons after injury, extremely little is known about how nerve cells respond to injury to their dendrites. For a tree, a trunk is necessary for a tree to survive, and damage to the trunk can be fatal – but it is equally true that branches and leaves are necessary for the tree to survive. What happens when dendrites are injured as can occur with trauma in either brain or spinal cord? Could a neuron regenerate dendrites after injury? If

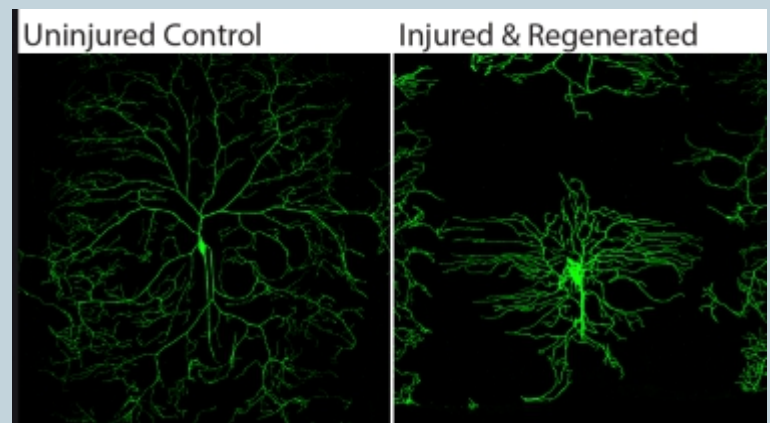
so, would the regenerated dendrite look like an uninjured neuron, or would it have the scars from injury?

Presumably, the reason why this fundamental question had been so little examined previously by scientists is because it is hard to selectively injure dendrites using traditional surgical techniques in rodent experiments. So Dr. Thompson-Peer took a different approach. Instead of using surgery, she developed a technique using lasers, that would allow her to very precisely injure individual branches of the neuron's dendrite arbor. She also adapted a model system that would allow her to follow the response to injury in individual neurons over time, so that she could longitudinally track how each neuron responded day by day to the injury. The model system is the beautiful net of sensory neurons in the skin of developing *Drosophila* (fruit fly).

Dr. Thompson-Peer discovered that soon after amputating a dendrite, sensory neurons initiated a growth response leading to dendritic regeneration. Interestingly, she also discovered that neurons regenerated the normal number of branches, but the branches appeared stunted, in the same way that a tree regrows shorter branches after pruning a “runner”. But, just like a tree that has regrown after pruning, the arbor didn't look like an uninjured neuron. The other really interesting discovery is that regenerating dendrites ignored cues in the environment that normally determine where branching occurs.

Regenerated dendrites were thinner, and the whole arbor was smaller and denser than an uninjured neuron. As a consequence, while the regenerated dendrites restored receptive function to the neuron, they only partially restored what had been lost (sounds a lot like axon regeneration failure). The neurons could receive information, but only about half as well as a normal neuron.

In her new lab at UC Irvine, as part of the RIRC, Dr. Thompson-Peer will be teasing apart the cellular mechanisms that allow neurons to regenerate dendrites and interrogating the factors that limit regeneration. What manipulations will allow neurons to regenerate dendrites more effectively?



Continued on facing page

Dr. Tom Lane returns to UCI



Long-time readers of Spinal Connections will remember Dr. Tom Lane--good friend, fantastic scientist and collaborator who was one of the original Associates of RIRC. Dr. Lane's research is on demyelinating diseases like multiple sclerosis and the role of the immune system in this devastating disorder. He's also interested in immunological deficits associated with spinal cord injury as well as the role of neuroinflammation in contributing to Alzheimer's disease.

Dr. Lane came to UCI in 1998 after completing a postdoctoral fellowship in neurovirology at the Scripps Research Institute. He rapidly rose to the rank of Professor of Molecular Biology & Biochemistry and Director of the MS Research Center. At Irvine, Dr. Lane was awarded a National Multiple Sclerosis Society (NMSS) Collaborative Center Award and a CIRM Early Translation Award to explore the therapeutic potential of neural stem cells in treating demyelinating diseases.

Dr. Lane has published numerous high impact papers using preclinical mouse models of MS. One of the major clinical features of mouse models of MS is paralysis due to demyelination of spinal cord axons, and Dr. Lane collaborated with Hans Keirstead and Os Steward on several papers related to the spinal cord.

In 2013, Dr. Lane was recruited to the University of Utah where he continued his groundbreaking research. However, his roots at UCI run deep, and so even while at the University of Utah, he continued his collaborations with Os Steward and Dr. Craig Walsh of the Department of Molecular Biology and Biochemistry. Now, we're delighted to announce that Dr. Tom Lane is returning to UCI as a Professor in the Department of Neurobiology and Behavior and RIRC Associate.

Tom will officially move his lab to UCI in January 2020, but we are already plotting an expanded collaboration.

Welcome back Tom!

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And, more broadly, are there circumstances or injuries or neuron types that are incapable of regenerating dendrites? Leveraging her training in neuronal development from the University of Pennsylvania, Johns Hopkins Medical School, and Harvard Medical School, bringing the tools to study dendrite regeneration that she developed as a postdoctoral fellow at UCSF, and funded by grants from the National Institute of Neurological Disorders and Stroke, Dr. Thompson-Peer is building a research lab to make significant advancements in this field. By addressing fundamental questions about dendrite regeneration, Dr. Thompson-Peer and colleagues hope to advance our understanding of how neurons can regenerate these essential cellular structures.

We're very excited to also announce that just before press time for this newsletter, the journal *The Scientist* highlighted Katie Thompson-Peer as one-of-ten rising stars in neuroscience.

Congratulations Katie!

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:
Krista Barajas, Reeve-Irvine Administrator
(949) 824-0210 or email k.barajas@uci.edu

Going viral: Amazing new technology allows delivery of gene-modifying cargoes to multiple spinal pathways after spinal cord injury

Sometimes there are technological advances that truly take us to a new playing field, and we've been lucky to be part of one this year. It's going to take a bit to describe the technology, so find a comfortable chair and settle in. But before getting into the weeds of the technology, let's set the stage in terms of what we need to repair the injured spinal cord.

We scientists tend to focus on paralysis because it's what is most obvious after spinal cord injury (SCI). Also, loss of ability to move and movement recovery are something we can measure and quantify in experimental animals, so these are usually the main "outcome measure" we scientists use for our spinal cord injury research programs. Our group's focus has been on the corticospinal tract (CST) which controls our ability to move voluntarily, and even short distance regeneration of CST axons could have a huge impact on quality of life for people whose hands and arms are paralyzed as a result of a cervical spinal cord injury (the most common type of injury in people).

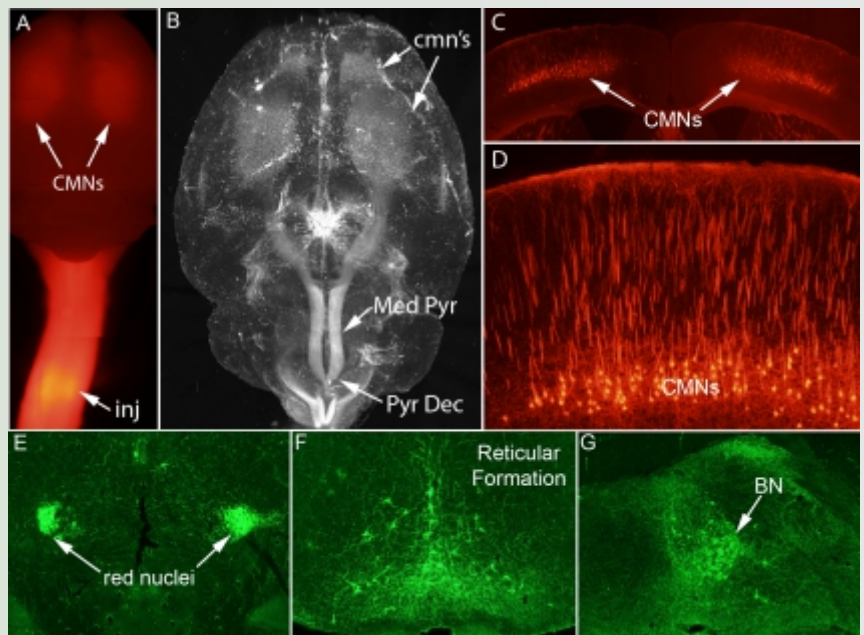
But all of you living with spinal cord injuries know that paralysis is only part of the story. Loss of ability to feel below the injury (loss of sensation) is important, and of course loss of bladder, bowel, sexual function and autonomic regulation of temperature and blood pressure are major problems that can be life-threatening. All of these functions are mediated by multiple different pathways from the brain to the spinal cord, and the greatest hope for recovery of multiple functions is to regenerate multiple pathways that are interrupted by SCI.

Now, on to the science:

Scientists at RIRC and throughout the world have been working diligently to find ways to stimulate regeneration of connections with some recent success. For example, our focus has been on using AAV vectors carrying shRNA to knock down the gene PTEN in cortical neurons to boost intrinsic growth capacity and thus stimulate regeneration of CST axons. We do this by injecting AAV/shPTEN into the cerebral motor cortex (see Anatomy 101, Fall 2018 issue of Spinal Connections). The limitation, however, is that we need to make multiple small injections to target a sufficient number of cortical neurons, and even then, we don't get to the neurons of other spinal pathways at all. So, the best we can hope for is regeneration of some CST axons, which is important, but only part of the answer.

The huge breakthrough that we've achieved over the past year is that we've been able to build on major discoveries in viral vector biology to develop a new type of AAV to deliver gene modifying cargoes to neurons whose axons are damaged by SCI.

This is called "retro-AAV", which has the remarkable property that it can be injected into the spinal cord, where it's taken up by axons and transported back to the cells of origin of spinal pathways in the brain.



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This is called retrograde axonal transport (the reason that the new AAV is called retro-AAV). Now imagine—instead of making injections of AAV into the brain, we can make a single injection into the spinal cord and the AAV with its cargo is transported back to neurons in the brain that give rise to multiple pathways that are damaged by spinal cord injury.

A picture is worth a thousand words, so here's the picture (Figure). In this study, we used a retro-AAV that expresses the enzyme Cre recombinase (retro-AAV/Cre) in our transgenic strains of mice. These mice are derived from the mice we used for our studies of regeneration enhancement with PTEN deletion. The mice are genetically modified so that when AAV/Cre transfects neurons, expression of Cre triggers a rearrangement of the mouse's DNA to delete PTEN and turn on expression of a fluorescent reporter protein called tdTomato.

Panel A of the figure shows an intact brain and spinal cord from a mouse with AAV/Cre injection at cervical level 5 (the bright spot in the spinal cord indicated by "inj"). Amazingly, you can see the glow from thousands of red fluorescent neurons that give rise to the CST (CMNs) in the intact brain. Panel B illustrates this brain using light sheet microscopy—another new technology we're deploying. For this, the brain is placed in chemicals that make it transparent, so now you can make out the milky way of light spots indicating individual neurons. There are about 25,000 transfected neurons in this milky way (about 80% of CST neurons are transfected). The individual CMNs are seen more clearly in slices through the brain (panel C and D).

The key thing is that neurons of origin of other spinal pathways are also transfected (shown in panels E-G in green fluorescence to highlight the fact that these neurons mediate other functions). For example, neurons in the red nuclei (E) contribute to voluntary motor function; neurons in the reticular formation (F) control walking and posture; and maybe best of all, neurons in Barrington's nucleus (BN in G) control bladder function.

So, now we are set to test whether it's possible to use the retro-AAV technology to trigger regeneration of multiple pathways after SCI to restore multiple functions including motor control of the hands and arms, walking, and yes, even bladder. Os Steward and his research team were awarded a new \$1.5million NIH grant in April, 2019 to further develop the retro-AAV technology for spinal cord injury therapy

If a picture is worth a thousand words, a movie is worth a thousand pictures, right? Actually, the image in panel B IS made up of over a thousand transparent pictures of slices through the intact brain taken with the light sheet microscope. The slices are then assembled into a 3D reconstruction (similar to an MRI) that you can rotate and see from different angles. If you want to see the movies of these reconstructions, links are on our website (Reeve.uci.edu).

We're really excited about this breakthrough and look forward to telling you more in future issues of Spinal Connections.

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

The Wet Weather Did Not Ruffle The Turkey Trot Feathers!



The weather outside was frightful, but the runners were so delightful! Over 800 supportive and enthusiastic runners attended the 2019 Plymouth Rock 'n' Run Turkey Trot. It was literally a deluge a few minutes after the start of the 10K/10 mile, but the turnout was fantastic. Thanks to the Plymouth Rock and Run team for a great Thanksgiving morning and thanks to everyone who participated to support spinal cord injury research at the RIRC.

Our Cause

The Reeve-Irvine Research Center is dedicated to advancing cures for spinal cord injuries, neuromuscular disease, and neurological disorders towards improving the lives of those who have experienced the debilitating effects of such injuries and illnesses. By exposing the value and urgency for such treatments, Plymouth Rock 'n' Run further strives to facilitate collaborative individual and business efforts, enhance the ideals of social responsibility, and promote social action to achieve improved health for a world-wide community.

Come trot with us next Thanksgiving!

Thursday, November 26th, 2020

Yorba Regional Park



THE CALIFORNIA STEM CELL RESEARCH, TREATMENTS, AND CURES INITIATIVE OF 2020: Renewed funding for the California Institute of Regenerative Medicine (CIRM)

Most readers of Spinal Connections are probably aware that the California Institute of Regenerative Medicine (CIRM) is in the final stages of funding grants from Proposition 71, passed by a substantial majority of California voters in 2014. At its October 31 meeting, the governing board called the “Independent Citizen’s Oversight Committee” (ICOC) approved \$32.92 million to fund CIRM's first clinical trial in Parkinson's Disease and to support three clinical trials targeting different forms of vision loss. This brings the total number of clinical trials funded by CIRM to 60 and expends all funds available for new projects except for the set aside for co-funding of projects on sickle cell disease in cooperation with the NIH.

A coalition led by Bob Klein, recognized as the primary driving force for Prop 71, has been working on a new initiative for the 2020 election, and on November 18, the coalition filed the final version with the State Attorney General as the first step in getting the measure approved for the 2020 ballot.

The new initiative is called “The California Stem Cell Research, Treatments, and Cures Initiative of 2020”. The full text of the initiative can be found on the Attorney General’s website. Some key provisions are:

- A. To Provide \$5.5 billion in bond funding to allow CIRM to continue funding stem cell and other vital research to develop treatments and cures for serious diseases and conditions.
- B. Dedicating \$1.5 billion for research and the development of treatments for diseases and conditions of the brain and central nervous system.
- C. Promoting accessibility and affordability of treatments and cures by ensuring that more Californians have the opportunity to participate in clinical trials expanding the number and geographic reach of clinics where specialized treatments and cures can be provided, including centers of excellence like Alpha Stem Cell Clinics and Community Care Centers of Excellence, and by helping California patients obtain treatments and cures that arise from institute-funded research and development.

There are also new provisions to enhance accountability and transparency, including rigorous conflict of interest rules and a cap on administrative expenditures to ensure that at least 92.5% of the bond proceeds are spent on research and the development and delivery of treatments and cures.

Bonds would be issued over a period of at least 10 years with payments postponed for the first five years and with total cost spread over a period of up to 40 years. The logic here is that the repayment is aligned with the period of time over which California patients are expected to benefit from institute-funded research.

The next step will be to gather the necessary number of signatures to qualify the initiative on the ballot.

One feature of the new initiative that’s particularly noteworthy is what is eligible for funding: “stem cell and other vital research”. Funds from the original Prop. 71 were almost entirely limited to stem cell research. It was only in 2019 that a project on gene editing was approved as a “vital research opportunity”, which required a 2/3 vote of the Grants Working Group. Eligibility as “vital research” in the 2020 proposition requires only a majority vote. Including other vital research is important because of the major strides being made to use gene modifying therapies to cure some of the most profound diseases and disorders.

Your Support of the RIRC Propels Vital Research Projects



Although we're proud of what we've accomplished in terms of advancing science over the two decades since the RIRC was founded, we still have a long way to go to improve quality of life for people living with spinal cord injury. Discoveries by RIRC scientists have formed the basis for clinical trials including the Geron-Asterias trial for stem cells, but it is clear that the therapy being tested will only be part of the answer, and will only apply to early post-injury setting. We need new approaches and innovative technologies to continue to advance therapies, especially for the chronic injury setting.

RIRC receives grants from NIH and foundations along with some limited funding from the university, but these are restricted to specific projects and/or activities such as education. Your generous unrestricted gifts are urgently needed to propel our science in ways that are impossible through grants and university funding, for example:

- To be used as seed money that can be rapidly deployed to test novel concepts and innovative approaches. Promising preliminary data generated with unrestricted funding is the necessary ingredient for grant funding from NIH.
- To support activities to launch collaborations including scientific workshops and visiting scientists whose direct collaboration brings new innovation. Scientists are often criticized for not collaborating, but collaborations are only launched when scientists are brought together. This is the primary goal of scientific workshops and visits by scientists from other institutions.
- To allow us to rapidly deploy new technologies.
- To provide fellowships for talented trainees who are not eligible for NIH fellowships. NIH fellowships are restricted to United States citizens, but science is a global enterprise and an important road to progress is to engage talented young scientists from other countries in the SCI research enterprise.

Your generous gifts can help change the future for people living with spinal cord injury.

Continued from facing page

This was highlighted in 2018 by accelerated approval of an AAV-based gene modifying therapy for spinal muscular atrophy (SMA), which is showing remarkable success in preventing disease progression and early death of children with SMA. Going forward, there may be other vital research opportunities for treating diseases and disorders that we can't even imagine today, as was the case for the development of iPS technology during the first round of funding from Prop 71.

Most readers will also know that Os Steward was a founding member of the ICOC and is one of only 3 original members who still serve on the board. As an ICOC member, Dr. Steward is prohibited from expressly advocating for the new ballot measure. If all of the above sounds dry and factual, this is the reason. Going forward, we will continue to provide informational material regarding the accomplishments of CIRM and the new ballot measure.



Reeve-Irvine Research Center

MEET THE SCIENTISTS EVENT

Saturday, March 28, 2020 | 12:00 - 2:30 pm

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.



**University of California, Irvine
Gillespie Neuroscience Research Facility
837 Health Sciences Road, Irvine, CA 92697-4265**



Wishing you the best for the Holiday Season

Reeve-Irvine Research Center, University of California Irvine

Image: GFP-labeled distal dendrites of neurons of origin of the corticospinal tract (CST).
GFP expression is induced by injecting retrograde-AAV/Cre into the spinal cord.

~ IRA Rollover Gifts ~



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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.



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www.plannedgiving.uci.edu



Reeve-Irvine Research Center

MEET THE SCIENTISTS EVENT

Saturday, March 28, 2020

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 // 11.26.20
yorba regional park // anaheim hills

plymouthrun.com

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



UC Irvine



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