

Spinal Connections

Reeve-Irvine Medal Symposium

“PAIN: MECHANISMS AND EMERGING THERAPIES”

Monday • October 23rd, 2017

University of California, San Francisco
Mission Bay Conference Center

Congratulations Reeve-Irvine Medalists



Allan Basbaum
UCSF



Claire Hulsebosch
University of Texas



Clifford Woolf
Harvard University

Speakers

Alban Latremoliere • Harvard University

David Luo • University of California, Irvine

Bhagat Singh • Harvard University

Edgar Terry Walters • University of Texas

Scott Whittermore • Whittermore University of Louisville

The Reeve-Irvine Medal Symposium

The Reeve-Irvine Research Center (RIRC) had the pleasure of hosting its Annual Medal Symposium, this year honoring

Dr. Allan Basbaum (UCSF), Claire Hulsebosch (University of Texas) and Clifford Woolf (Harvard University),

On October 23rd, 2017 at the University of California, San Francisco.

The Reeve-Irvine Medal Symposium was a full-day event and it focused on

“Pain: Mechanisms and Emerging Therapies”.

For information on the Reeve-Irvine Medal Symposium please contact Dr. Mariajose Metcalfe at metcalfe@uci.edu

Distinguished speakers and discussion topics

| | | |
|---------------------|--|--|
| Claire Hulsebosch | The University of Texas Health Science Center at Houston | Persistent Inflammation and Pain after Spinal Cord Trauma |
| Allan Basbaum | University of California San Francisco | Cell Transplants to Treat Chronic Pain |
| Clifford Woolf | Harvard University | Teasing out drivers of pain and their consequences |
| Bhagat Singh | Harvard University | Exploring chemotherapy induced peripheral neuropathy |
| Alban Latremoliere | Harvard University | Modulating Pain Through Sleep |
| Edgar Terry Walters | The University of Texas Health Science Center at Houston | Persistent nociceptor hyperexcitability induced by SCI: Doleful consequences, hopeful implications |
| Scott Whittermore | University of Louisville School of Medicine | Proteostasis as an end global therapeutic target for CNS injury |
| David Luo | University of California, Irvine | Abnormal synaptogenesis in neuropathic pain development |



In this issue...

| | |
|--------------------------|-------|
| Dr. Harriet Chang | Pg 4 |
| Brain Computer Interface | Pg 5 |
| RIRC Alumni | Pg 6 |
| Meet the Scientists | Pg 7 |
| Funding Research | Pg 11 |

Update on stem cell trials for spinal cord injury



Dr. Oswald Steward

There is continuing positive news for the clinical trial being conducted by the company “Asterias” involving transplants of oligodendrocyte precursor cells (OPCs) derived from human embryonic stem cells. In this “Director’s Column”, I try to present things in a conservative and cautious way, but the latest news is really exciting and points back to fundamental discoveries here at the RIRC.

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).

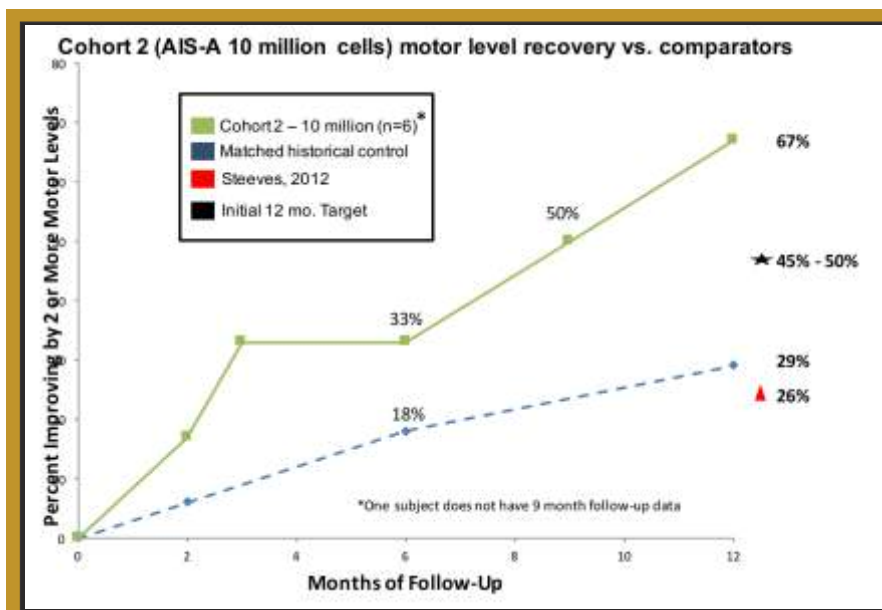
After a lot of preclinical work, the clinical trial for oligodendrocyte precursor cells (OPCs) was launched by the company “Geron” and was the first ever trial for human stem cells for spinal cord injury. This trial was terminated for economic reasons and the company Geron folded but the company “Asterias” was founded and re-booted the trial with their product called “AST-OPC1”.

Since our last newsletter, the company has continued to provide interim reports on the results of the trial involving 6 subjects with cervical level injuries that had received 10 million OPCs (called “cohort 2”). These subjects had shown improvement in arm, hand and finger function at 3-months and 6-months following treatment, and the 9 month data showed more improvement. Then, just as we were finalizing this article in early October, Asterias released 12 month data on the 6 subjects in cohort 2. There was additional motor improvement so that 4 of the 6 subjects (67%) now exhibited at least two motor levels of improvement over baseline on at least one side and one achieved 3 motor levels of improvement on one side. This extent of recovery is higher than what would be expected based on independent data for historical controls. It’s important to emphasize that regaining two motor levels can improve ability to perform daily activities like feeding, dressing and bathing and reduce the overall level of assistance the person requires.

An article in the San Francisco Chronicle by Erin Allday quotes lead investigator, Dr. Richard Fessler, Professor of Neurosurgery at Rush University Medical Center: “Scientifically, I have to say we don’t know for sure if it’s the stem cells. But I’ve been treating these kinds of patients for 30 years, and I’ve never seen anything like this before.”

Although the current reports are very exciting, it’s important to keep in mind that the treatment being tested is only a start. If this was a computer application, you could think of this as version 1.0. The original science documented a measurable but modest improvement in motor function in rats, but with this as a start, we can move on to find better and more effective therapies (version 1.1, 1.2, etc.).

With an eye toward the need to develop more effective treatments in the future, it’s useful to look back at the roots of this story because it highlights the huge impact of private donations. The initial research by Dr. Kierstead’s group



The RIRC Welcomes New Faculty Member

Dr. Harriet Chang



Dr. Chang has been working in the urological fields for over 10 years. Her predoctoral training was with Dr. William C. de Groat, who is recognized as one of the world leaders in research on neural control of bladder function.

Dr. de Groat received the Reeve-Irvine Research medal in 2009 for his fundamental studies in this area. Dr. Chang's expertise is in pharmacological modulation of bladder function following spinal cord injury (SCI). Her studies focus on rodent models, and the control of a muscle called the external urethral sphincter. To void the bladder in a normal way requires that two physiological actions occur simultaneously. The bladder (which is actually a muscle) has to contract and at the same time, the external urethral sphincter, which is basically a biological valve, has to open. These two actions have to occur in "synergy" (which means together). People who have suffered a spinal cord injury often suffer from a condition called "dys-synergia", in which there is bladder contraction triggered by a full bladder at the same time that the sphincter (the valve) doesn't open. This causes a pathological increase in pressure within the bladder, which pushes urine back up into the kidneys. All of this greatly increases the chances for kidney damage and urinary tract infections. Thus, figuring out how to control the external urethral sphincter is of great importance.

Dr. Chang is currently funded by NIH/NIDDK to investigate the urethral function by using spinal cord epidural stimulation (SCS) in the rodent model of SCI. SCS is a well-developed and widely used technique on neuromodulation, especially for neuropathic pain and the recent studies of locomotion. Dr. Chang first used this technique on modulation of urethral sphincter focusing on the improvements of voiding function in rodents with SCI.

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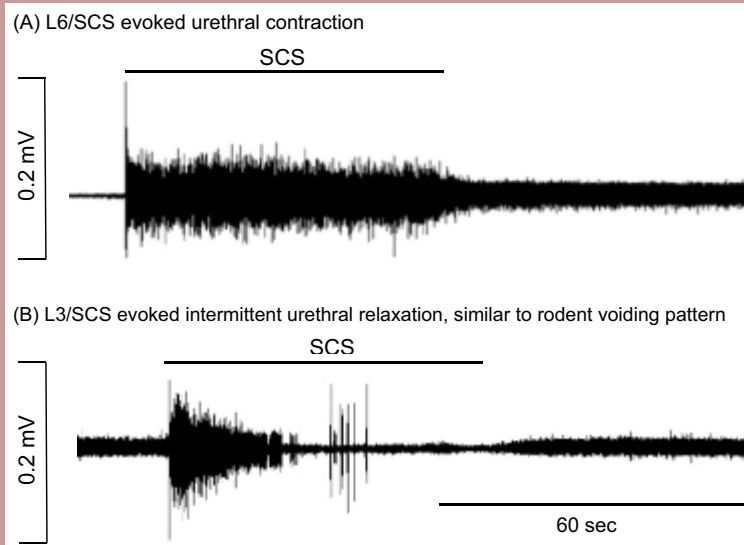


Figure 1: Representative examples of urethral activation elicited by SCS on L6 (A) and L3 (B) spinal segment in intact rats. L6/SCS evoked only EUS tonic contraction showing the increase of urethral resistant. L3/SCS evoked the urethral relaxation, which is similar to the rodent voiding pattern.

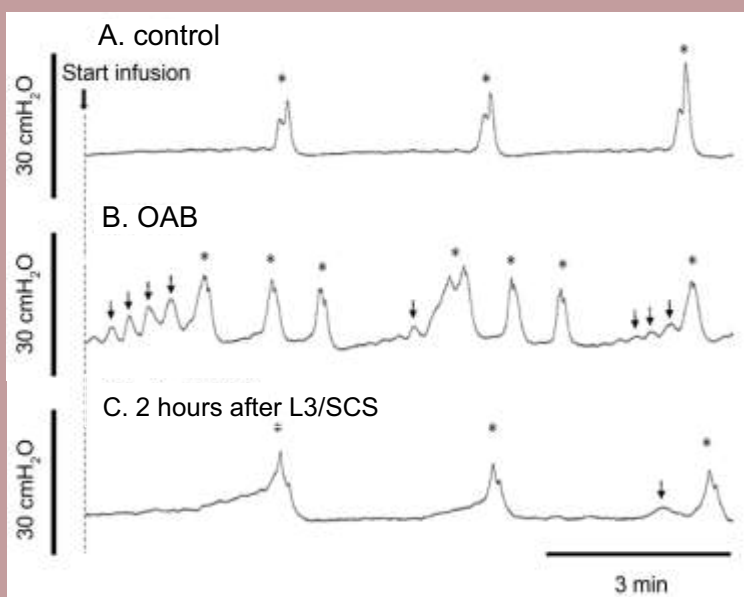


Figure 2: During bladder infusion, the control rat (A) showed the regular voiding (*). The OAB rat showed the frequent voiding with non-voiding contractions (arrows). L3/SCS (C) ameliorated the OAB symptoms by increasing the bladder capacity and reducing the non-voiding contractions (arrows).

UCI heads \$8 million NSF-funded project to develop brain-computer interface

Implantable technology to restore sensation and walking in spinal cord injury patients

The National Science Foundation has awarded \$8 million to a consortium led by the University of California, Irvine to develop a brain-computer interface that can restore walking ability and sensation in individuals with spinal cord injury. This initiative represents the largest NSF award received by faculty researchers in the UCI engineering and medicine schools. "The goal of this multidisciplinary project is to create an implantable system that by circumventing the damaged portion of the spinal cord can enable patients with these injuries to regain feeling in their legs and walk again," said principal investigator Payam Heydari, UCI professor of electrical engineering & computer science.

"Spinal cord injuries are devastating and have a profoundly negative impact on independence and quality of life of those affected," he added. "These resulting disabilities cost the U.S. roughly \$50 billion per year in primary and secondary healthcare expenditures, so we hope that our work can solve a major national public health problem."



The five-year grant, sponsored by the NSF's Cyber-Physical Systems Frontier program, will be divided among UCI, California Institute of Technology and the University of Southern California. Heydari's co-principal investigators on the project are Zoran Nenadic, UCI professor of biomedical engineering; An Do, UCI assistant clinical professor of neurology; Richard Andersen, the James G. Boswell Professor of neuroscience at Caltech; and Charles Liu, professor of neurological surgery at Keck School of Medicine of USC.

Nenadic said that the UCI research team has been working in recent years

to miniaturize brain-computer-interface systems, shrinking them from the size of a desktop computer to pacemaker scale. Nenadic and Do collaborated previously on a proof-of-concept study to implement a brain-computer interface which enabled a paraplegic man to walk a short distance. The goal of this new NSF-funded project is to perfect the technology and decrease its size.

"Professor Heydari's lab, which specializes in low-power, nano-scale electronics, designed and implemented several critical integrated circuits that makes scaling to this small size possible," he added.

This new initiative will focus on converting existing technology into a fully implantable version which will be implemented in a manner similar to deep brain stimulators. To test the technology, the UCI team will collaborate with Caltech and USC on clinical studies in volunteers with spinal cord injury. "Since these systems are fully implantable, they will be inconspicuous, work around the clock and access much stronger brain signals, facilitating highly accurate control of movement," said Nenadic.

Do, an expert in neurorehabilitation, sees potential beyond helping individuals with spinal cord injury. "Once these systems are FDA-approved, their application can be expanded to people affected by disability due to stroke or traumatic brain injury," he said. "The study also will greatly expand our knowledge of how the human brain controls walking and processes sensation – knowledge that can help researchers better understand disease processes that affect these functions."

The Cyber-Physical Systems Frontier program is one of the largest within the NSF, providing funding for major efforts that identify and address critical problems which have the potential to be solved through the use of electronic, computing and information technologies.

Reeve-Irvine Research Center Alumni



Jessica Nielson, who received her Ph.D. with Os Steward in 2012 and then went on to a postdoctoral fellowship at UCSF with Adam Ferguson at UCSD, has been appointed as an Assistant Professor of Psychiatry at the University of Minnesota. Congratulations Jessica!



Rafer Willenberg, who received his Ph.D. with Os Steward completed medical school at UCSD and won appointment to the prestigious Neurology residency program at Cedars Sinai Medical Center. Congratulations Rafer!



Harriet Chang, Ph.D., who was a postdoctoral fellow at RIRC with Leif Havton, has returned to RIRC as an Assistant Professor of Urology (see article on page 4).



Brian T. David, PhD, completed his graduate studies at the University of California, Irvine in the Reeve-Irvine Research Center. He was recently appointed as an Assistant Professor and Laboratory Director in the Department of Neurosurgery at Rush University. Congratulations Brian!



Erin Gutilla, Ph.D., completed her Ph.D. on schedule in April of this year. The title of her dissertation was: "Approaches to promoting mTOR-mediated growth and regeneration in the mature central nervous system". Her dissertation research has led to 2 publications so far with one more submitted. Erin returned to medical school in June and is completing her clinical rotations. She'll graduate with the dual degree (M.D., Ph.D) in 2019. Congratulations Erin!!!



Reeve-Irvine Research Center

MEET THE SCIENTISTS EVENT

Saturday, March 17, 2018 • 12:00 - 2:00 pm

University of California, Irvine



With Special Guest Nitin Bhatia

Associate Professor of Clinical Orthopaedic Surgery
Interim Chair of Department of Orthopaedic Surgery
UCI Hospital

Dr. Bhatia, a Board Certified Orthopaedic Surgeon and Fellowship Trained Spinal Surgeon, serves as Director of the Combine Spine Program and Chief of Orthopaedic Spinal Surgery Service at the University of California Irvine Hospital. Dr. Bhatia specializes in the surgical and non-surgical treatment of spinal disorders. He has a special interest in problems affecting the cervical spine as well as spinal trauma. He also has significant experience with the thoracic and lumbar spine and with minimally invasive procedures.

Dr. Bhatia has been featured as a treating surgeon in the television show "Guardian Angels, MD" seen nationwide on The Learning Channel (TLC) as well as programs on PBS. He has expertise in all areas of spinal pathology including spinal stenosis, disc herniations, spine trauma, scoliosis, complex cervical and lumbar reconstruction, and failed back syndrome. Dr. Bhatia has completed multiple spine surgery fellowships and has trained in both orthopaedic and neurosurgical techniques. Dr. Bhatia is a member of multiple international and national spine related organizations including the North American Spine Society and the highly selective Cervical Spine Research Society which has less than 20 members in the state of California.

Dr. Bhatia graduated with honors from Stanford University, after which he attended Baylor College of Medicine in Houston, Texas. During medical school, Dr. Bhatia won numerous research awards and was the valedictorian of his graduating class. Following his Orthopaedic surgery residency at UCLA, Dr. Bhatia completed a spine surgery fellowship at the University of Miami/Jackson Memorial Hospital, after which he completed a second spine surgery fellowship at Miami Children's Hospital. Dr. Bhatia is active in multiple research projects including federally funded spinal cord injury research and has been nominated for the prestigious Russell Hibbs research award by the Scoliosis Research Society.

For info go to www.reeve.uci.edu or email tania.jope@uci.edu



Meet the Scientists Event 3•11•17



Congratulations Reeve-Irvine Medalists



Oswald Steward
- Reeve-Irvine Research Center

Allan Basbaum
- UCSF School of Medicine

Clifford Woolf
- Harvard Medical School

Claire E. Hulsebosch
- The University of Texas
Health Science Center at Houston

Jim Swinden
- President of the Irvine Museum

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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

FROM THE *Director...*
CONTINUED FROM PAGE 3

at RIRC was supported in part by private donations to our Center. One major finding in the original paper was that OPC transplants during the “acute” post-injury period improved function whereas transplants into rats with chronic injuries didn’t. We were able to do the study of chronically-injured rats because the animals had been generated for our summer boot camp “Techniques in Spinal Cord Injury Research”. We were able to maintain the rats into the chronic period because of private donations.

Private donations were critical for the initial pilot experiments that provided critical preliminary data for grant proposals. The first actual grant to support the work came from the “Roman Reed Spinal Cord Injury Research Act” and then Dr. Keirstead received a research grant in the initial round of funding by CIRM to support his stem cell research at RIRC. And of course, CIRM funding has been critical for the clinical trial by Geron and then Asterias.

To put all this in perspective, it’s worth remembering that when the RIRC was launched in 1999, there were no ongoing trials for people with SCI. We’ve come a long way and there is great optimism that we are on track for even greater advances. However, private donations are still the most important driving force for the first stage of innovation.

Dr. Harriet Chang

Continued from page 4

The use of SCS over the upper lumbar cord (L3) evokes the urethral relaxation (Figure 1). This technique improves the voiding efficiency and promotes urine expulsion in the rodents with dys-synergia after SCI.

Dr. Chang’s team also applies L3/SCS to investigate the effect on bladder overactivity in rodents. Overactive bladders (OAB) has the symptoms including frequent bladder contractions, urgency and urine leakage, commonly seen in people over 40 years old and men with prostate enlargement. L3/SCS increases the bladder capacity and decrease the bladder contractions (Figure 2).

Dr. Chang wishes to establish the foundation for studies of mechanisms associated with bladder dysfunction and contributes to improve voiding efficiency. Dr. Chang will explore new therapeutic approaches to these problems using pharmacological modulation and artificial electrical stimulation.

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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Plymouth Rock 'n' Run is brought to you by ResearchforCure,
a 501(c)(3) charity supporting spinal cord injury research
at the Reeve-Irvine Research Center (RIRC), UC Irvine



Generosity

Leaving a Legacy of Hope

"From a tiny acorn grows the mighty oak." Like the acorn in this old maxim, regardless of the size of a bequest, it can grow into a lasting legacy.

In August of this year, the Reeve-Irvine Research Center was the beneficiary of a generous planned gift from Albert N. Goldfeder. This gift established an endowment in Mr. Goldfeder's name that will exist in perpetuity at the RIRC along with \$40,000 for current use for public educational programs and scientific symposia and to support pilot research studies on innovative approaches to improve function after spinal cord injury. Mr. Goldfeder will be publically acknowledged for his generosity at the 2018 Reeve-Irvine Research Medal Symposium (see cover article), which will be open to the public. His generosity has opened the door to so many opportunities for our Center, providing funding to accelerate discovery, but also allow for flexibility to rapidly address new opportunities.

A bequest is one of the easiest forms of gifts that you can make to support the Reeve-Irvine Research Center. Through your bequest, you have the opportunity to establish a lasting legacy that offers hope to thousands, and to shape the lives of future generations. Planned giving is a way to remember a friend or relative, fulfill a desire to help others less fortunate or give back to the community, or make an investment that will grow knowledge and advance science. Your donation could lead to a key discovery that will be linked to your contribution forever! And of course, planned giving can bring important tax benefits.

Every dollar makes the research go further, faster.

Below are some examples of ways planned gifts make a difference.

- Seed Money for new 'out of the box' research ideas, support for new projects that are spinoffs of existing projects to improve the quality of the potential treatment, as well as advancing projects that are underfunded. These pilot studies will provide critical preliminary data for future grant proposals.
- Accelerating progress - exciting new studies may have funding that is distributed over years but the studies could be done more quickly. You who are living with SCI want rapid progress and our researchers are ready and able to move research forward without delay to test potential therapies. Any research project requires technical support; lab items must be ordered, finances must be tracked, animal research protocols must be prepared, and progress reports are required. Funds that are restricted to research cannot be used for these critical support services. Some equipment may be too costly for standard grant applications and/or may be restricted to one specific project. Bequeathed gifts allows for cross use of equipment maximizing impact not only in the immediate future but in perpetuity.
- Public Events- give an opportunity for those who suffer with an SCI injury to speak directly to our scientists to ask questions about their injury and to see first-hand the latest research that is being conducted through on-site tours.
- Scientific Symposia- Scientific meetings are one of the primary venues for scientists to share their findings before publication and establish new collaborations. This is a key to the process of science that leads to innovations that come from thinking as a team.

All of us at the Reeve-Irvine Research Center would like to send our heartfelt thanks to the Goldfeder family. It is private gifts like his that play a critical role in propelling spinal cord injury research programs and explore creative opportunities that cannot be explored through traditional funding sources. We are grateful to Mr. Goldfeder for his interest and support of the RIRC.

Funding Research

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a501(c)(3) charity supporting spinal cord injury research
at the Reeve-Irvine Research Center (RIRC), UC Irvine



UC Irvine



Reeve-Irvine Research Center

MEET THE SCIENTISTS EVENT

Saturday, March 17, 2018

12:00–2:30 pm

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



With Special Guest Nitin Bhatia

Associate Professor of Clinical Orthopaedic Surgery
Interim Chair of Department of Orthopaedic Surgery
UCI Hospital

For more information go to www.reeve.uci.edu
or email tania.jope@uci.edu

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