Aileen Anderson, Ph.D., and her science team at the University of California Irvine (UCI) have joined the Reeve International Research Consortium on Spinal Cord Injury. The Consortium, the centerpiece of the Foundation’s research portfolio, comprises seven neuroscience laboratories in the United States and Europe that collaborate on therapy development for spinal cord injury (SCI).

Anderson is no stranger to the Consortium. Indeed, she has been part of it since the beginning. Each Consortium lab is led by a PI, or principal investigator; each PI enlists a group of younger scientists – graduate or postdoctoral students – called Associates. These early-career researchers deal with the day-to-day symbiosis between Consortium labs. Anderson, then a post-doc studying Alzheimer’s disease, was the Associate in the lab of Carl Cotman, Ph.D., also at UCI. This exposure to spinal cord research had a profound impact on Anderson’s career path. She has since dedicated herself to the development of therapies for SCI.

In 2001, in parallel with setting up her own laboratory, Anderson became scientific director of the Foundation's Animal Core Laboratory at UCI. The Core is akin to an animal model SCI research co-op; it facilitates research by individual Consortium laboratories, and helps set up collaborative experiments between two or more Consortium labs. It also is a training venue for Associates (and in a twist, last year Anderson hosted postdocs from other former Associates’ labs for a week-long immersion in the art of doing spinal cord research). Anderson, now a PI, will continue to head the Core lab.

Science is not just a job for Anderson. It’s more of a lifestyle. Her closest colleague at UCI is Brian Cummings, Ph.D., who happens to be her spouse. The couple met as undergraduates at the University of Illinois at Urbana-Champaign; both got their doctorates at UCI. They live close enough to their labs to walk to work; they have a daughter, Camryn, 7.

Anderson spoke recently with Reeve staff member Sam Maddox.

Kudos for being named to the Consortium. What does it mean for you personally, and professionally?
This was a huge thing for me, really a huge accomplishment. The Reeve Consortium is a group of very established senior investigators for whom I have always had an incredible amount of respect. On a personal level, it was really gratifying to be considered worthy to be among that group. From a professional level, getting a steady level of support for a PI to run a laboratory is always a difficult task, so to have the Foundation support, and to have access to the collaborative network and the incredible work being done in the Consortium – it is phenomenal. It opens up many kinds of experiments and collaborations. It’s very exciting.

Tell us how the Consortium works.
The Consortium has always been collaboration-driven. There are other consortia in science that are more free-for-all but this one was built to be a network where people work together doing complex, multi-disciplinary projects that you might not do otherwise. The Consortium runs in three-year cycles and as a part of a renewal process we all just went through, the PIs in the various labs established our top priorities for spinal cord injury research for the next three years, and what experiments we are going to do together, building on this unique network of expertise and technical knowledge.

Your perspective on the Consortium is unique. How has it evolved over the years?
This was the first network of its kind. It was an experiment by what was then the American
Riluzole May Be Neuroprotective; Second Phase of Clinical Trial Set

Riluzole, the first spinal cord injury (SCI) therapy tested by the North American Clinical Trials Network (NACTN), has been shown to be safe, and early results show the drug may help patients regain some motor function. The results of the Phase 1 clinical trial, which was sponsored by the Reeve Foundation, have been submitted for publication.

Robert Grossman, M.D., professor of neurosurgery at The Methodist Hospital Neurological Institute in Houston and principal investigator of NACTN, and PI on the safety study, said of the results, “We don’t want to over-advertise the Phase I results, or to claim too much. But there were no serious adverse events in the first study and the data are encouraging; we are eager to move to a larger trial.”

Riluzole, already approved by the Food and Drug Administration for the treatment of amyotrophic lateral sclerosis (ALS), appears to be neuroprotective if administered within 12 hours of injury. A Phase II/III trial is planned to evaluate the drug in a much larger patient sample.

NACTN was created by the Reeve Foundation to speed the testing of potential therapies for SCI in a coordinated, multi-center setting. NACTN is a consortium of 10 neurosurgery departments, a data management center, and a pharmacology center. The network hopes to bring recent molecular and cell-based discoveries in neuroprotection and regeneration into clinical trials.

NACTN has been supported by the US Army Medical Research and Materiel Command, which recently announced its continued support for the Network and the riluzole trial with a $2 million contract.

The Phase II/III trial – called RISCIS, for Riluzole in Spinal Cord Injury Study – will include 350 patients with cervical injuries, the group that seems to benefit most from the drug, at as many as 20 clinical centers. The trial is being led by Michael Fehlings, M.D., Ph.D., professor of neurosurgery and medical director of the Krembil Neuroscience Center at the University of Toronto and sponsored by AOSpine North America (AOSNA), in partnership with the Reeve Foundation and NACTN, as well as AOSpine International.

“Riluzole appears to be safe in traumatic acute spinal cord injury, and the progress of neurological recovery appears promising,” said Fehlings. “In the Phase I riluzole group, 50 percent of patients with complete motor and sensory injuries – ASIA A patients – converted [improved to ASIA B, or incomplete] compared to only 25 percent in a group not treated but matched with NACTN’s large registry of controls.”

The Phase I trial included 36 patients with traumatic acute spinal cord injury from C4 to T12. Most patients were male (83 percent) and had a cervical injury (78 percent). All were treated within 12 hours of injury. Riluzole, 50 mg, was administered enterally (tablet form) every 12 hours for 14 days.

The drug is thought to work by blocking sodium channels, which in turn reduces the influx of calcium ions and thus prevents the stimulation of glutamate receptors; excess glutamate can be toxic to nerves. The drug is “ideally suited as an early-phase treatment in spinal cord injury,” according to Fehlings.

The Phase I patients that seemed to improve most were ASIA Bs, those with some spared sensory or motor function. Fehlings said riluzole also seems most neuroprotective in cervical patients, probably for reasons of anatomy and the fact that these injuries tend to be “low energy” and therefore offer more opportunity for protection.

The RISCIS trial, set to begin this summer, is expected to take two years to enroll all patients. Grossman said recruitment is generally not difficult; the drug involves no surgery or other invasive procedures.

He also noted that one critical thing the larger study hopes to learn is how a particular dosage of riluzole correlates to motor function outcome. “All medications have a window for dose response. We don’t know what that is for this drug. But one of the advantages of NACTN is that we have a pharmacology group, in Houston, that can help us establish the relationship between the blood-level of riluzole and clinical outcome.”

Ultimately, said Grossman, riluzole is not likely to be a “magic bullet” type treatment. “The real hope is that the drug will provide some neuroprotection, and then if we can add a regenerative strategy to that – anti-Nogo [nerve growth promotion] or even stem cells – we can enhance recovery. The less severe the injury, the better the recovery. That may seem obvious, but we hope riluzole can prevent some damage so that a regenerative treatment can work better.”

The RISCIS study is being funded collaboratively by Department of Defense support for NACTN and by AOSpine, an international education and research society of 6,000 spine doctors that has funded studies related to the spine, such as arthritis, spinal cancer, spinal deformity and trauma.

AOSpine was founded in 1958 by four neurosurgeons from Switzerland. They used royalties from surgical tool innovations to create a foundation. “AOSpine is very interested in spinal cord injury trials,” said Fehlings. “Along with NACTN they have specific expertise and methodology to conduct trials.”

Fehlings noted that while clinical trials are quite costly to run, the collaborative infrastructure of NACTN allows for great savings. “A trial the size of RISCIS would be expected to cost $30 million,” he said. “We will be able to complete the trial for about $4.5 million. Because of our efficiencies and electronic data capture systems, the savings will be dramatic.”
Epidural Stim Update: Four Subjects, Trending Positively

Four individuals have now been fitted with epidural stimulators and undergone aggressive Locomotor Training in a research project at the Frazier Rehab Institute in Louisville, KY, under the direction of Susan Harkema, Ph.D., who also directs the Reeve Foundation NeuroRecovery Network. While only the data on the first subject, Rob Summers, has been published in the medical literature, Harkema reported at the Society for Neuroscience meeting last fall that the second and third subjects, both completely injured, responded to the epidural stimulation in a surprisingly positive way, much the same as Summers did. A fourth person has also been implanted with the stimulator; no results have been made public.

Epidural stimulation is the application of continuous electrical current to specific locations on the lower spinal cord, at T11-L1. This location corresponds to neural bundles in the cord that control movement of the hips, knees, ankles and feet. Epidural stimulation is thought to mimic signals the brain normally sends to initiate movement. Once that signal is provided, the spinal cord’s own neural network – plus the sensory input derived from the legs to the spinal cord – directs the muscle and joint movements required to stand and step with assistance on a treadmill.

As was widely reported in 2011, Summers regained significant motor function with the stimulation turned on. He could stand and bear weight; after a few months of intense Locomotor Training, he could also move his toes, ankles, knees and hips. What’s more, he recovered bladder, bowel and sexual function, even when the stim was off.

The research team was surprised by the voluntary recovery of function; they suggest the epidural stimulation may have awakened residual but weak spinal nerves. The recovery may also have been the result of nerve regeneration or sprouting as a result of repetitive activity-based training.

Other subjects in the experiment have also reportedly shown unexpected recovery. New Mobility magazine recently quoted one of the latest patients, Kent Stephenson, 25, of Mount Pleasant, Texas, injured at T4 in a motocross accident in 2009. Without stimulation: no movement, no control. Stimulator on: “I could just feel a tingly rush all the way down my body,” said Stephenson. He was asked to move his knee toward his chest (while lying down). “It just came right up. It was…insane. I was just smiling from ear to ear.” Stephenson, too, reports bladder improvement and enhanced sexual function. “I’d go back and do it over any day, any time.”

Harkema cautions that it is too soon to draw conclusions. “But we are encouraged by the results of our first four patients. While publishing is forthcoming, a clear trend has been seen toward similar responses to stimulation.”
Paralysis Association, before it became the Reeve Foundation. The experiment was to say, spinal cord research isn’t working as a field, we need to find a way to jump-start it by pulling in new people if we’re really going to make progress. The original Consortium was populated largely by labs that didn’t do spinal cord research – at all. There were two or three PIs who were bona fide spinal cord researchers, who had injury models in their labs and routinely worked on SCI. The other founding labs were very well-known, very well-respected, but not for spinal cord work. So the goal was to get people from outside the spinal cord field to apply their expertise and to think collaboratively about the problem and how to solve it. Now, the Consortium is a network of people where everybody fundamentally does SCI research. There is a depth of research now – in part due to the success of the Reeve Foundation in planting the seeds for spinal cord injury research to evolve as a field, thus increasing the number of labs.

Collaboration is the mantra now. Was it a natural thing in the early days? The dynamic was very different back in the 1990s. People were eager to bring their A games, making sure they were well-perceived by their colleagues, and they brought their new exciting research data. But there was some anxiety – you lay out unpublished data on the table that someone could pick up and run with, that requires a certain amount of trust and respect, and that developed over time. There is much less anxiety now. There is a very natural and comfortable interactive feel within the Consortium that reflects the maturity of the group. It is amazing to be involved.

So the Consortium labs bring their A games, and they don’t mind showing their cards? Exactly. It is extremely rare in our meetings for one of the Consortium labs to share data that has been published. Those unpublished data are cards you usually hold closer to your vest.

The Associates’ program has been a big success, as many of these folks, such as yourself, have gone on to form their own labs and expand the field. It was a remarkable opportunity. We were surrounded not just by an incredible set of investigators who where very high on the achievement scale, but the people they brought, the other Associates, were fantastic too. Bouncing ideas off one another and talking about collaborative experiments – it was fun and very stimulating, especially to do that in a free environment, without worry that someone would run off with an idea. We’d get critical feedback about our science, which was invaluable. But one of the things I learned as an Associate, and what I try to convey to my lab now is, the importance of asking the critical question, the one that moves the field forward. The Consortium taught me to not just run around in a circle asking small incremental things, but to ask the question that was going to make a difference, that was going to give us an advance. There’s a certain level of maturity necessary in science to get to that perspective, and the PIs in the Consortium all had it, and they conveyed it to us Associates. That’s a big level up in terms of your thinking, scientifically. So, any Associate will tell you, being part of the Consortium was a tremendous influence on their career and for their scientific thinking and maturity; it certainly was for me.

And now you have your own Associates … Right. People from my lab get to come and have the same network of training and experience that I did. I brought my first set of Associates to a Consortium meeting earlier this year – they came back just completely blown away. I remember that feeling. They had a blast, and they learned so much in that short meeting.

The kinds of research questions you are asking… how about a snapshot of your current science? My lab has two main tracks, one is about role of inflammation and the innate immune response and the complement cascade – what goes wrong and what goes right after spinal cord injury. That
“... the biology told us that early was not so good and later was probably better ... Our goal is to push that boundary into the truly chronic range.”

is a track I started as an Associate – and it’s really coming along fantastically. It is a very difficult set of experiments – it’s been great to have Ben Barres (Stanford) come in to the Consortium. He has an interest in inflammation and complement and so we dovetail in our thinking and interactions. Right now, one of my graduate students is looking at how inflammatory proteins interact in the spinal cord injury microenvironment [the complex biochemical milieu of cells and molecules, the extracellular matrix where they reside, plus the various mechanisms for interaction] and influence things, not just in clearing debris or the classic things we think of but actually modulating the environment and promoting regeneration. This is a cool story – it’s not just about what goes wrong, as in the role of inflammation in degeneration; it’s more complicated. These proteins might also be promoting recovery of function.

The other part of what we do is look at different kinds of stem cells, and how those cells, particularly neural stem cells, interact after injury. We are especially interested in the microenvironment and how it affects the cells, and how the cells influence the microenvironment to yield recovery of function. We have a number of stem cell projects underway. One is focused on neural stem cells that are in a spinal cord clinical trial now in Switzerland, and we’re evaluating how those same cells will work in a cervical model of injury.

We work with a lot of kinds of stem cells – embryonic and induced pluripotent (iPSC) derived cells. We’re trying to understand when we make those cells how they respond to the microenvironment. Do induced cells behave the same as tissue-derived stem cells? Or are they lacking some of the molecules and the signaling pathways needed for them to respond in the same way? We have seen some really striking differences between tissue-derived and iPSC stem cells. If we can understand this, we might be able to get the iPSC cells to do a better job integrating into the microenvironment and yielding repair.

OK, tell us about the clinical trial of your stem cells.

Mind you, these are not my stem cells. They are StemCell Inc.’s cells. They came to us, early on, and said, ‘Hey would you like to take a look at these stem cells?’ The great part of that story is that I said, ‘No, I’m starting up my lab, I don’t have enough time.’ They said, ‘No, we’d really like to fly down and talk to you.’ I said, ‘OK, I can give you an hour on Thursday.’ They said, ‘We understand you are using some unique injury models; we think this is really the only place we can test our cells. Would you hear us out?’ So they came down and I knew enough about stem cells at that point to realize that their stem cell population looked very different, and very interesting, compared to other stem cells lines I had seen. The context is that at the time we started this work, when I was an Associate in the Consortium, very few people did mouse models of spinal cord injury. One of the things I wanted to do with our studies was to ask questions in transgenic animals, and for that you had to go to mice. That’s why they came to us. To test their human cells they needed an immune-deficient animal and there were very few labs you could go to for that. In the end, they convinced me to do a pilot experiment.

We did some animal transplants; we looked at the data and thought, that’s pretty cool. Then we did the next study and the next, and the next thing you know, here we are 12 years later. It’s an interesting process; it starts out as basic science, and as you get indications of efficacy and things are looking solid, now you have to transition. The company is no longer just looking for basic science, they’re doing what they have to do to move things forward, on an intellectual property level, and into clinical trial, because that’s their ultimate goal. Thirty years ago that didn’t happen very often. Now, with the translational mindset of NIH, and within the scientific community, we all are more conscious that we can’t stay locked in our labs forever. There is a drive to move things into the clinic. The give-and-take between companies and a lab in an academic setting is challenging ground to navigate.

So the trial continues, in Zurich and soon in Canada … and there are hints of recovery.

Right. The trial will enroll 12 subjects total – people injured from three to 12 months. One must keep in mind this is an open-label, single-site trial, Phase I, Ia, so this is a very early stage in terms of looking at things. Enrollment of the ASIA A patients [complete loss of sensory and motor function] has been completed. And that’s where there are some initial reports of sensory function that looked very promising, very interesting, but again, it’s early stage data.

What’s in progress now is recruitment and enrollment of incomplete subjects for that trial. It’s challenging to do that; it is a lot for people with recent spinal cord injury to think about, whether to participate or not, but I am hopeful we will be able to complete the trial. I really think there is the most potential in the incomplete cohort. But the only way to know is to test it in people.

The word ‘chronic’ has not been heard much in clinical trials. It’s good news.

Yes. There are a number of therapies that lots of labs are developing for spinal cord injury now. Fundamentally, it really depends on what the biology is telling you. In the case of the tissue-derived StemCells Inc. cells, in terms of transplantation, the biology told us that early was not so good and later was probably better.

In our preclinical work now the goal is to push that boundary into the truly chronic range. One, because it’s a better place to do a clinical trial. If you can enroll people with a stable baseline there is consensus that would be a better place to be able to assess the difference made by a potential treatment or therapy. The other thing, from an ethical point of view, is getting good informed consent – allowing people enough time to think about getting an experimental treatment, to see where they are going to plateau (in the natural course of recovery after their injury) before they rush down this path.

You have the busy career, the family, the California lifestyle to maintain. How do you manage?

Ha. Sometimes better than others. How does anybody manage? I think I’m really lucky in that Brian is also a faculty member at UCI and a collaborator – we’ve worked on these projects together for a long time. For many professional couples, if you’re coming across disciplines, it may be hard to get your head around what the other person is up against in terms of their responsibilities, what deadlines they have that week. It’s a big advantage for us in that Brian and I can download relatively quickly and prioritize between us. OK, your emergency trumps my emergency – today – so I’ll go pick up Camryn and walk the dog and do the other stuff that needs to be done, and then we trade that back the next day. It helps us both keep some balance in terms of life outside academia.
CONSORTIUM ADVISORY PANEL
CAP provides counsel to the Foundation’s Board with respect to the International Research Consortium on Spinal Cord Injury.

Albert J. Aguayo, M.D.
Director, Center for Research in Neuroscience
Montreal General Hospital, Montreal

Fred H. Gage, Ph.D.
Professor, Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases
Salk Institute for Biological Studies, La Jolla, CA

Robert G. Grossman, M.D.
Director, The Neurological Institute
Chairman, Department of Neurosurgery
The Methodist Hospital, Houston, TX

Louis F. Reichardt, Ph.D.
Professor, Physiology/Biochemistry/Biophysics
University of California, San Francisco

Charles H. Tator, M.D., Ph.D.
Professor of Neurosurgery
University of Toronto
Toronto Hospital, Western Division

SENIOR MANAGEMENT
Peter T. Wilderotter
President and Chief Executive Officer

Maggie F. Goldberg
Senior Vice President, Marketing and Communications

Susan P. Howley
Executive Vice President, Research

Aimee B. Hunnewell
Vice President, Development

Niketa Sheth
Senior Vice President, Quality of Life

PROGRESS IN RESEARCH
©2013 Christopher & Dana Reeve Foundation
636 Morris Avenue, Short Hills, NJ 07078
Toll-free 800-225-0292
www.christopherreeve.org

Produced and edited by Sam Maddox and Susan Howley

Special Thanks
Progress in Research is made possible through a generous gift from Hank and Charlotte Stifel.

many of the researchers on the team. We told them about life with a spinal cord injury and gave detailed accounts of our daily lives, such as how important it is to maintain our skin, bladder and bowel health, and the challenges people living with paralysis encounter on a daily basis. We explained how our injuries have changed over time and how we have adapted to those changes. We discussed how inspiring it is to see such amazing research, considered science fiction not long ago.

We concluded our visit with an architectural tour of the iconic Salk Institute and saw the amazing Dale Chihuly glass sculpture there. Most of us living with spinal cord injury understand that we are unlikely to be "cured" someday with a magical treatment. However, we hope that treatments will be developed to give us incremental recoveries. Any type of improvement in feeling or function could dramatically affect the quality of our lives. If, for example, Stefan could gain movement in his hands and fingers, his quality of life and ability to function independently would dramatically improve. If I could get off the ventilator and breathe on my own, or gain some upper arm function, I would no longer need 24-hour care and would be far more independent.

Stefan and I have confidence that the research we saw will, with time and effort, lead to treatments for people living with spinal cord injuries. We cannot express enough our gratitude to Dr. Pfaff and all the researchers who have dedicated their lives to understanding spinal cord injuries and the nervous system. Every researcher is contributing to the vast body of knowledge that is bringing us one step closer to practical treatments.

Ed. note: Mark’s and Stefan’s visit affected our view of research and personalized the hard work being done in the labs. The visit was inspiring for the host scientists, too. Here is an excerpt from a note by Marito Hayashi, a grad student in the Pfaff lab:

I think it is easy for scientists to lose sight of the big picture of research by being too caught up in our everyday routine experiments. Getting to know Mark and Stefan made me take a step back.

I used to feel hesitant connecting my research to clinical/therapeutic applications or specific people/patients because I can’t guarantee that what I work on will improve their lives. My personal joy in science is the process of coming up with ideas, thinking logically, and conducting experiments that may lead to mechanistic insights into biological phenomena. But I felt today the visitors had deep understanding of how research goes; they shared their positivity and wisdom with us, and gave me a new perspective. I am truly grateful for the opportunity I was given today.
Twice a year the scientists of the Reeve International Research Consortium on Spinal Cord Injury meet face-to-face to share their latest studies and to oversee their various collaborations. Most recently, the Consortium gathered in Santa Monica, CA. Included were the principal investigators (PIs) from the seven Consortium labs, plus their Associates – the graduate students or post-graduates who manage the day-to-day lab operations.

As is the custom at these gatherings, the Associates meet alone as a group on the first day. They share the details of their work and collaborations, and often dream up new ways to work as a team, across labs.

This time, the group of 20 or so Associates boarded vans for a field trip to the campus of UCLA, home base for Consortium member Reggie Edgerton, Ph.D., and his Associates, Prithvi Shah and Guillermo Garcia-Alias. Edgerton’s lab studies the role that training and activity have in shaping the spinal cord circuits that generate posture, locomotion, and fine motor skills. Work here forms the basis of the Reeve NeuroRecovery Network, and the exciting experiments with epidural stimulation (see page 3).

Edgerton introduced one of his primary collaborators, Yuri Geraskimenko, visiting from Moscow. Dr. Geraskimenko presented an overview of his work with stepping function and brain stem stimulation.

Later, the Associates toured the Edgerton labs and saw firsthand the animal models that are the basis of the lab’s restorative strategies for spinal cord injury. They also toured new facilities being staged for clinical studies to better understand how spinal cord circuitry can be modified and restored.

The following two days the Consortium met in full, with more detailed show and tell and discussion about research projects. The Associates were each called upon to present their latest data and face the scrutiny of the experts -- not just from the PIs, but also from the esteemed panel of Consortium Advisors.

On the final evening the Consortium hosted a dinner for Foundation donors and members of the Los Angeles spinal cord community. Each PI presented a snapshot of his or her work, and made themselves available to chat with the guests and answer specific questions about research and the potential for recovery after spinal cord trauma. (See page 3 for more about one of these interactions.)
Dr. Barres Named to National Academy of Sciences

Ben Barres, M.D., Ph.D., a member of the Reeve Foundation International Research Consortium on Spinal Cord Injury, has been elected to the prestigious National Academy of Sciences (NAS), “in recognition of distinguished and continuing achievements in original research.”

This is one of the highest honors a scientist can achieve. NAS members are nominated and extensively vetted by their peers. NAS has about 2,200 members in the United States and 400 from other countries. About 200 NAS members have won the Nobel Prize.

Says Barres, a professor and chair of the department of neurobiology at the Stanford University School of Medicine, “This was a total surprise.” He said that personally, his election to the Academy was a “nice honor. But the primary significance to me is that it matters for young people. It sends a strong message to them that our country really values science and that they should consider becoming scientists.”

The Barres lab studies glial cells, the support cells in the nervous system, astrocytes and oligodendrocytes, that change, in good ways and bad, in response to injury or disease. To fully understand how recovery after spinal cord injury can occur, it is essential to know how glial cells operate, and how it might be possible to modify their behavior and affect the process of disease, or the process of repair after trauma.