ALEXANDRA REEVE GIVENS: BROAD APPROACH TO CARE, CURES

Alexandra Reeve Givens has been on the Board of Directors of the Reeve Foundation for nearly five years. She’s played an indirect role in the Foundation for much longer than that, since the time of her father Christopher’s spinal cord injury. Alexandra was 12 then; she was schooled in disability lifestyle issues and even some basic neuroscience by her very knowledgeable dad. Along with older brother Matthew and her stepmother Dana, she came to understand firsthand the issues that make paralysis a family issue.

Alexandra, who is articulate as she is graceful, has become the public face of the Foundation, often appearing in news articles and television interviews. Alexandra, married and a practicing attorney in New York City, spoke recently with Reeve staff member Sam Maddox.

What is the Reeve Foundation about, in a nutshell?

As an organization we are obviously focused on science, on finding cures for spinal cord injury but also on providing care for people living in the here and now. I think that’s a powerful combination, the most effective way the Foundation can offer help to the community. We are bringing together cutting-edge scientists and promoting collaboration but we’re also supporting numerous organizations around the country and spreading our network out so we can improve the quality of life of people living with paralysis.

In older days, people thought of cure as getting a treatment leading to some huge recovery. That’s not the way it’s coming, is it?

What we are learning is that there are going to be many types of cure, many cures, for people with different levels of injury, and for different completeness of injury. And for that reason we pursue an array of different scientific approaches. I think that is really the strength of our research program. We are working with scientists who are attacking the problem from all sides, looking at all possible solutions.

Your dad was extremely well-informed and totally focused on the research side. He knew the scientists, read the journals, knew what was what. Do you try to do that?

I try to but it’s difficult. There is so much information out there. And for people without a science background, like me, it’s difficult to wade through it all to see what’s true and what’s not, what’s just Internet speculation. An important role for the Foundation is to help people filter through that information and focus on what the really exciting areas of research are.

Stem cells, for example – here’s an issue surrounded by lots of information and misinformation.

What people have to realize is that we are taking many approaches to research, that it’s not just about stem cells although we certainly do invest in this field. We’re excited about two scientists within our Research Consortium who are using stem cells as a way of better understanding the spinal cord, and the daunting problem of why it does not spontaneously regenerate by itself.

Continued on page 4
James Fawcett runs one of the six labs that form the Reeve Foundation International Research Consortium on Spinal Cord Injury. His lab is located at Addenbrooke’s Hospital at the University of Cambridge, in England, and is part of the Center for Brain Repair, an institute formed in 1995 and funded by the British Medical Research Council.

Dr. Fawcett started his career as a doctor, working in the autoimmune disease area, including very tough conditions such as systemic lupus. “One of the things about being a doctor, you eventually become competent at what you are doing. For some people, that’s great. Others might feel, ‘what’s new? I don’t want to do this for 40 years.’ I decided I wanted to start doing research.” One of Fawcett’s options was to stay in the area of autoimmune diseases. “It’s an interesting field and would have been an easy move but at the time, the basic immunology science was not in place to ask sensible questions about how to address autoimmune problems. Indeed, nothing much happened in that field until the immunology caught up with it just five or six years ago.”

Fawcett had an undergraduate interest in nervous system development and followed that toward a Ph.D.; he then had the choice: clinic or lab. “I enjoyed the science so much I decided to do that. But having been a doctor, one is always thinking about treating patients in the end. I felt that if we can understand how the body first makes a brain and nervous system, maybe we can understand how to fix it. It was a no-brainer to go into neuroregeneration.”

Dr. Fawcett went to work on one of the central issues in spinal cord science: the environment of the spinal cord is inhibitory to axon regeneration. “So the first experiment I did was to look at the different sorts of glia [support cells in the nervous system] to see which ones were inhibitory. My first paper was on oligodendrocytes, the next one was on astrocytes. I discovered that Martin Schwab [an original member of the Reeve Consortium whose lab is in Zurich] was well away with the oligodendrocyte story [having discovered the inhibitory substance Nogo] so I decided to stick with astrocytes and the glial scar.”

In about 1990 Dr. Fawcett set out to show that astrocytes in the glial scar could block regeneration. “That wasn’t straight forward so we had to develop a sort of three-dimensional tissue culture model. The next step was to demonstrate that inhibitory molecules were found in the extracellular matrix [the molecules that surround living cells, offering support and cohesion]. We were able to identify these as chondroitin sulfate proteoglycans. These are the inhibitory molecules I’ve been working on pretty much since then.”

Dr. Fawcett’s lab then showed that these proteoglycans could be digested with the enzyme chondroitinase. “By doing this we could remove the inhibition and thereby allow axons to regenerate in the spinal cord.” At the time the field was aware of chondroitinase, which helps break down sugar in proteoglycans, but, says Dr. Fawcett, “It had not been appreciated for its role in removing inhibition.”

There was more to the enzyme than inhibition. “To our surprise the axons recovered much faster and much better than they should have given the amount of regeneration we observed. At that point we realized that chondroitinase could also stimulate plasticity; indeed, we felt plasticity must be its main mode of action rather than regeneration.”

The Fawcett lab took out a patent on
using chondroitinase for axon plasticity. The U.S. biotech company Acorda Therapeutics licensed the molecule for potential clinical use. Regulatory and safety tests are moving forward for a clinical trial in the not-too-distant future.

 Says Dr. Fawcett, “We have a huge amount of animal data but still have to do a lot of safety work to determine the final formulation. And we have to figure out how to best administer the enzyme. Typically, in animals, we inject it either directly to the spinal cord or in larger quantity around the cord. In humans, though, the cord is much larger; the enzyme cannot diffuse very far, so you cannot put it in the fluid surrounding the cord and expect it to get into the middle. That means we probably have to inject it; one is cautious about putting needles into the injured spinal cord.”

 An enzyme that helps dissolve scar and boosts plasticity at the site of injury, does this look like a potential therapy for chronic SCI? That’s not clear, says Dr. Fawcett. “We know we can give chondroitinase to rats one month after injury and it works pretty much the same as in an acute animal. Whether that means it will work in a very chronic animal we don’t know. For people, our view is that chondroitinase needs to be given at the same time as rehabilitation is going on. The two have a positive interaction. Rehab usually begins at three weeks or so after injury, and that would be a good time to do the chondroitinase treatment.”

 The way chondroitinase enables recovery, Dr. Fawcett suggests, is by forming “bypass circuits.” The spinal cord is very rarely severed, he said, which means there are almost always a few fibers that survive the injury. “Plasticity in this case means that fibers above the lesion area make connections to interneurons which project through the region. Or, undamaged axons below the lesion make new connections – in the nervous system there appear to be a lot of synapses that are non-functional. It could be that they are activated by sprouting, which is activated by the chondroitinase. By opening up the silent synapses, a bypass is formed.”

 “One certainty in any clinical trial for chondroitinase is that it will be accompanied by rehab. “In our various experiments to show that chondroitinase stimulated plasticity, we found that using it in combination with rehab improved efficacy.”

 Recently, the Fawcett lab found other beneficial effects for chondroitinase. “A cartilage type structure called the perineuronal net forms around some neurons and seems to turn off their plasticity,” said Dr. Fawcett. This is not related to trauma but to age. “This net forms after about the age of five – we’re very plastic as young children; we can recover from many types of trauma.” Chondroitinase removes these nets.

 Also, chondroitinase makes it easier for implanted cells to migrate and integrate within the spinal cord: Chondroitinase is being used in experiments in other labs using various combinations with implanted Schwann cells or stem cells. For example, Dr. Charles Tator’s lab in Toronto, funded by the Reeve Foundation, is using chondroitinase along with neural stem cells and a scaffold structure (see p. 10).

 Combinations are an active area of research, says Dr. Fawcett. He is currently conducting a large collaboration with the Consortium’s Schwab lab to test chondroitinase along side the anti-Nogo antibody [which removes the Nogo inhibitor]. “It is too early to be sure but initial results look like there is an additive effect.”

 About one-third of the Fawcett lab is working on plasticity. Another third is on a different angle: understanding why nerve fibers themselves lack the ability to grow. Dr. Fawcett is ready to move on: “My view of the inhibition molecules, the scar, chondroitinase, Nogo, the rest of it, is that we’ve kind of done that. We’ve found the inhibitory molecules and know what to do about them. The problem we have to solve now is that nerve fibers are not very good at regeneration; they are intrinsically poor at it. We are looking at ways to fix that.”

 In work that has not yet been published, the Fawcett lab found a very specialized filter at the initial segment of the axon. “A lot of the molecules you need to make an axon grow are getting blocked at this point. Once a neuron matures, this filter kicks in – molecules that used to get in to the axon to make it grow in the embryo are suddenly no longer there. The axon is simply not equipped with the right molecules.”

 Others in the Fawcett lab are going in another direction, working on a neuro-electrical interface to facilitate bypassing spinal cord injury by taking signals from the brain or spinal cord above the lesion to control muscle or a prosthetic below. Said Dr. Fawcett, “All of this works quite well except at the interface with the nervous system. Interfacing electronics and the nervous system, that’s the unsolved problem. The prosthetics are coming along well, and the software is getting pretty sophisticated. It is our view that it is no good having a prosthetic if the brain can’t control it.”

 Dr. Fawcett envisions the eventual answer to treatment of SCI as a combination biological repair plus prosthetics. “Biologic repair is never going to be complete; it will mostly be focused on the area of the spinal cord fairly close to the injury. That means the prospects for people to get back arm control are pretty good. But I don’t think the prospects are as good for walking, regaining bladder or sexual function. Those connections are an awful lot further down the spinal cord.”

 The Fawcett lab was invited to join the Reeve Foundation Consortium “out of blue,” said Dr. Fawcett. Setting up a collaboration enriches and expands the field but it doesn’t necessarily happen on its own. Said Dr. Fawcett, “It’s not so much an issue of trust, rather it’s an issue of getting to know what the possibilities are in each lab. You can’t interact with someone unless you have a clear idea of what the other lab is doing. These are big labs but as we meet and share data, we eventually learn what’s going on. Then you listen. You hear something, aha, that relates to a problem I’m trying to solve, you pick up on it, and you have a collaboration.”

 Fawcett recently completed a collaboration with the Consortium’s Mendell lab, in Stony Brook, NY. “This was a collaboration experiment with growth factor in their lab and chondroitinase from our group. We wanted to see if there was a combined effect. There was. We also found something unexpected: in the undamaged area around the spinal cord all the nerve fibers stopped conducting action potentials. This conduction block had not been seen before. We were even more surprised to see that chondroitinase could relieve the conduction block and allow axons to carry on. This finding helps explain why a number of nerve fibers near the injured area don’t seem to be working, even though their anatomy looks okay.”

 Dr. Fawcett is a busy investigator with many non-science obligations. “It’s a sort of Catch 22,” he said. “You are hired because you can do experiments but you do fewer of them as you become more senior and successful. It is a bit frustrating. I love doing experiments. I don’t get to have as much fun.” — Sam Maddox
are using stem cells not as therapeutics but as research tools – for example, creating human spinal cord circuitry in a Petri dish in order to test potential new therapies. This kind of scientific innovation will create a solid foundation upon which future stem cell therapies can be built.

Sure, we want to motivate people and spread the message that stem cells are an exciting field, along with a lot of other areas we are working in. But we have to advocate for responsible science and for responsible education of the spinal cord community about new therapies, including stem cells. People must understand that research takes time and that there are no quick fixes: it must be done rigorously and responsibly. That is one of the challenging things about our work.

That is where the North American Clinical Trials Network [NACTN, say ‘nack-tin’] plays such an important role. We have set up a network of hospitals that can conduct clinical trials and determine safety and effectiveness as we test different therapies. That’s such a critical thing; you must establish benchmarks. What is so amazing is that by creating NACTN, the Foundation has put in place the people and expertise and infrastructure needed to conduct spinal cord injury clinical trials. As we progress with the research we can move seamlessly from the bench to the bedside. This is very exciting and NACTN is a very important resource for the entire spinal cord field.

And this is also where the NeuroRecovery Network figures in, yes?

The whole area of activity-based therapy, including body-weight support treadmill training, this is a really exciting avenue. We are seeing almost everyone who goes into the NRN program getting some level of recovery. For some, it’s improved health benefits, regulating blood pressure, getting improved circulation. For a few, it’s the regained ability to stand or step. If locomotor training improves an individual’s core strength, the results can be life-altering.

As a member of the Board, do you get an inside look at the research portfolio?

It’s actually my favorite part of board meetings. We are of course concerned about organizational structure and other aspects of the Foundation. But Arnie Snider, vice chair of the board and chair of the Research Planning Committee of the board, and Susan Howley, executive VP of research, present the work that our grantees are doing. They also present the recommendations of our Science Advisory Counsel, the Consortium Advisory Panel and the NeuroRecovery Network Advisory Panel. We hear about the latest developments and the grants we are funding. Often times we will have a researcher come in and present his work to the board – which is just so motivating. As a board it’s our responsibility to translate what’s happening in the room that day, and to think big picture, the impact it is going to have in the community, what scientists need from us and the role we can play. The same is true when members of the community who are living with paralysis come speak with us. These exchanges give us a shot of energy.

What is the best way to move toward the big picture, with an honest yet aggressive approach in funding big science?

It’s a balance. The field is incredibly exciting now. Amazing things are happening and a myriad of new ideas are coming about. We are there to support and provide infrastructure, and to help bring scientists together so they can collaborate and share ideas in ways they might not as they can sometimes be siloed in their own labs. It’s also important that we at the Foundation are the guardians or custodians of the message and help provide guidance to people living with paralysis – they want information on what to hope for and when to hope for it. Our website does a good job, and so does our Paralysis Resource Center, in spreading that message and providing some benchmarks so people are given a clear, measured understanding of progress and understand precisely what the therapies are ... and are not.

What kept the Foundation together in the years after your dad and Dana died?

One of the key things after we lost dad and Dana was realizing, within our leaders and main spokespersons, that it is up to us as a community to fill that gap. One of our priorities has been to build the infrastructure to facilitate that shift. We now have strategic fundraising alliances across the country and we are really expanding our base. My older brother Matthew and I founded what’s called the Champion’s Committee, which is a young person’s fundraising initiative. Team Reeve is growing and growing each year. What it comes to is realizing it’s all of us contributing, even if it’s five dollars at a time. The population is so large, there are 1.275 million Americans living with spinal cord injury. We can do this, we can fund this research, if everybody comes together and contributes.

That number, 1.275 million, was quite a surprise...

It was so fascinating that we really had not taken the time to calculate the numbers of people with paralysis before. I was lucky enough be part of the group that went to D.C. to present the new numbers. We hosted a press conference and were able to speak to people about this. To suddenly have the data to back this up – you thought 275,000, it’s 1.275 million. The looks on their faces when they saw the size of that... it was really powerful. The number of people living with paralysis, not just spinal cord injury but other causes as well, that’s 5.6 million, and it’s important for us to recognize that community. We are not just about spinal cord injury. We are about opportunities and quality of life for people living with all types of paralysis. That’s a big community and if we can speak with a powerful enough voice we can make a real difference.

The Quality of Life program started in your living room, didn’t it?

I remember when I was a kid, Dana used to work on the floor of our living room, that was her work style. She would sit with this huge stack of quality of life applications. And be inspired but so frustrated. For everyone you fund there are 10 you turn away, and it’s heartbreaking. We still have that problem. The solution is to go out and raise more money so we can fund more programs.

I have personally passed out Quality of Life grants, and while the dollars are not huge the impact is, leveraging greater community support.
That's really what we see the quality of life program doing. It's providing seed money to organizations. We carry over the same idea in research grants. It's an ethos of the Foundation: we have the resources to invest in new programs, in start-ups, to think creatively about the grants we give. People can leverage the Reeve stamp of approval to then go out and get more funds in their community. It means we get a huge return on our investment. It makes our organization more powerful and it means we spend the money we have wisely.

We have developed a rigorous system for application reviews, for monitoring how grantees spend their awards and then for reporting after the fact, what the returns have been. We help them leverage our funds; we give them, for example, a press kit to go out to the community and make our grant into a bigger return, to get more donors invested in their program as well. The other thing, once they get money from us they can't apply for three years. That supports the seed model as well.

One of my favorite examples of our Quality of Life program involves a cooperative of people living with physical disabilities, some have brain injuries, some spinal cord injuries and they came together and wanted us to help them obtain a printing press so that they could start a business together. We bought them an accessible printing press. The whole idea is that they don't have to come back to us for money, we've given them a leg up. Now they are able to go out and raise money themselves, and to provide their own income. Not many organizations are going to say, how can I help a group of 15 people with disabilities ... it's not intuitive but we were able to step in. It's so empowering, and it's getting people back to the workforce. It's really where we're all about, getting people back into the community, helping them support themselves.

Employment remains an area of much concern in this community.

Right, especially when you see the numbers – two-thirds of families' household income is less than $25,000 a year. Going back to the workforce, for dad, that was the most important thing. To be sitting in rehab, thinking what am I going to do next, thinking, I'm going to be defined by more than this. He was able to work with the Foundation, and lucky enough go back to directing and acting. He got so much value from that, and to continue to support our family, be the breadwinner, that meant an awful lot to him. And it was a blessing for our family; we realized how lucky we were. Many others don't have the same opportunities.

The Foundation plays a role in advocacy, what are the areas of concern?

I see the paralysis prevalence study as a major piece of advocacy because it provided Congress and others with the numbers they need to help talk about why we should care about this issue and this community. Of major concern is working to influence that federally funded spinal cord research continues unabated. We need to keep getting out there to spread the message so we stay on the public agenda. For the NIH, for example, or the Department of Defense. We do get a lot of government funding now. Support from the Centers for Disease Control and Prevention is the lifeblood of the Foundation’s Paralysis Resource Center, which is an incredibly important part of what we do. And CDC funding, combined with some private donations, funds our quality of life programs.

We are also working with the Department of Defense on the research side. Think about the armed forces and those coming back from Iraq and Afghanistan with so many different kinds of horrific traumatic injuries – this is an issue that's very important to us. The Foundation is committed to supporting our wounded military men and women who are dealing with the same issues civilians living with paralysis deal with, including the potentially life-threatening secondary consequences of SCI, access to the best physical therapy, challenges returning to the workforce, insurance and accessibility issues. That's where the Paralysis Resource Center comes in, providing a vital lifeline.

What is the pitch to sell the message?

Part of the sell has to be encouraging people to take a long-term view: If you invest in medical research and treatments now it's going to save so much money down the road. And it's also making sure people realize that when we talk about cures we don't mean The Cure but rather increased recovery at any level. Even an incremental gain can make such a material difference in people's lives, in their ability to return to work, to support themselves, to enjoy improved health outcomes.

The notion of what is a cure, this was a big issue for dad. People always say, you talk about the cure and you'll be off and running a marathon. For him, it was wanting to be off the respirator, to go from 24-hour round-the-clock nursing care, never being on his own, to being able to breathe independently and therefore being incredibly more self-reliant.

A large part of the Reeve Foundation effort is around building collaboration...

The idea of collaboration works for us at every level of the Foundation. We are starting to collaborate with other groups that fund spinal cord injury research. We all have the exact same goal. We want the same things. So if we begin to pool our expertise and our resources and to be judicious about investing our money, the multiplier effect can have a powerful impact on the field.

We are of the mindset that if you can gather like-minded, inspired people in a room, great things are going to happen. We believe we are innovative and creative in the way we fund spinal cord research so that we maximize our precious dollars and the world's scientific brain power and we get the best returns and the best results. We are trying to use every dollar so wisely.
The Reeve Foundation hosted its fourth Spinal Cord Symposium, From Bench to Bedside, in December in Phoenix, AZ. The gathering, from Friday evening until midday Sunday, offered a broad showcase of the work funded by the Foundation.

The symposium assembled 120 scientists across many disciplines who are supported by Reeve funds. Scientists go to lots of meetings, but what makes this one unique is that the researchers are not only talking and sharing ideas among themselves but with what might be called their shareholders: people affected by paralysis who are counting on them to find treatments and therapies. Some 60 or so members of the SCI community were included in the weekend’s activities – bringing real-world relevance and a sharper sense of urgency to the work of the researchers.

From the non-scientist’s perspective, the Symposium offered an unfiltered and even intimate look into the process of discovery, and a deeper appreciation of the complexity of spinal cord biology and the intricate sorts of problems researchers are consumed by.

This gathering was remarkable on another level: for the first time, scientists and clinicians from all four Reeve research programs participated. The first three symposia (Chicago, Boston and Atlanta) focused on science from Individual Research Grant awards; the Phoenix meeting also included senior scientists and members of the Reeve International Research Consortium as well as leaders of two other Reeve initiatives, the North American Clinical Trials Network and the NeuroRecovery Network. The Symposium was also attended by six members of the Reeve Foundation Board of Directors.

Dr. Albert Aguayo of McGill University opened the meeting on Friday evening with the keynote lecture, “A Look Back at Regeneration.” Aguayo, who is on an Az symposium: scientists meet their shareholders

Albert Aguayo, like all scientists, stood on the shoulders of those who came before him. Most notably for Aguayo, it was the work of Santiago Ramón y Cajal in the late 1800s that inspired him. Using modern tools and staining methods, Dr. Aguayo built on Cajal’s Nobel-Prize-winning work. It was at Aguayo’s lab in Montreal in the 1980s that spinal cord nerve fibers (axons) were coaxed to grow for the first time, but only within the permissive environment of a peripheral nerve graft. Aguayo’s group also showed that, in the optic system, regenerated axons from the central nervous system could indeed re-form functional connections.

The impact of this work has been enormous. The Aguayo lab’s groundbreaking discoveries ignited the field of spinal cord injury research. The notion that the environment of the damaged spinal cord was toxic to axons led to the detection of molecules within the cord that actively stop nerve regeneration. These inhibitory molecules are today the focus of numerous experiments as scientists attempt to neutralize them and thereby promote axon growth. At least one such molecule, Nogo, discovered by the Reeve Consortium lab of Martin Schwab in Zurich, has entered into a clinical trial for acute SCI.

Susan Howley, executive VP, research at the Foundation, has worked closely with Dr. Aguayo since 1995 in his role as a member of the Foundation’s Research Consortium Advisory Panel. “In addition to his spectacular science, he is a wise and witty counselor, unfailingly honest and patient. His views are always tempered with a generosity of spirit and great good humor. As befitting someone who has made such seminal findings in the field of regeneration, his wisdom and occasionally unique perspectives invariably enrich the task at hand and open new vistas for contemplation and action.”

Albert Aguayo: A Huge Impact on Spinal Cord Science

Albert Aguayo, Ph.D.
advisory panel that oversees the Reeve Consortium, paid homage in his talk to the scientific lineage that informed and shaped his own work. Aguayo made particular reference to Spanish neuroscientist Santiago Ramón y Cajal, whose theories in the late 1890s paved the way for much of what is understood today about lack of recovery after SCI.

At the reception following his talk, Aguayo, in his grandfatherly manner, chatted with old friends and sat with new ones, continuing his tutorial on the history of spinal cord science. Meanwhile, scientists caught up with colleagues and engaged the members of the community in the basics of neurobiology. The community, in turn, engaged the scientists in the basics of living with paralysis.

Saturday was a full day of science. The morning’s sessions included a very fundamental look at successful axon regeneration from the perspective of the lowly (but quite instructive) *C. elegans* worm, as well as a look at regeneration of axons that control breathing, and at regulation of axon growth by growth cone manipulation.

Later Saturday morning, Leonard Lopate, host of WNYC’s “The Leonard Lopate Show” hosted a Town Hall meeting, considered by many attendees as the highlight of the weekend. This forum addressed the issues of families and caregivers, the unsung participants in a loved one’s spinal cord injury story. Prompted by Lopate’s easy manner and insightful questions, a mother and son, husband and wife included the many expenses of disability – both financial and emotional – as well as shrinking access to health care and equipment, and more and more issues with insurance benefits and reimbursement. Lisa described moving to Massachusetts for better health care coverage; her doctor, Steve Williams, explained how his hospital, Boston Medical Center, struggles to deliver proper care but loses money delivering services that don’t get reimbursed.

Marilyn Hamilton urged the scientists to “hurry it up. The work you do is mind-baffling but we are grateful for it. But I’m getting older now.” She also urged the community to step up its advocacy efforts, to educate and inform the public, policymakers and the health care community.

Saturday afternoon included concurrent chalk talk breakout sessions, which are not large formal “show and tell” scientific presentations but rather smaller, more intimate opportunities for investigators to present their data on a specific topic and then engage with their audiences in lively discussion. Topics included stem cells and SCI, “waking up the sleeping spinal cord,” improving respiration and dealing with the inhibitory extracellular matrix in recovery.

On Saturday evening, Dr. V. Reggie Edgerton (UCLA) gave a lecture entitled, “It’s Time to Pick the Fruit.” He was introduced by Arnie Snider, vice chair of the Reeve Foundation Board of Directors, whose brief remarks set forth the challenges for a scientific movement making the transition from research to clinical application. Snider, schooled in the ways of Wall Street and private enterprise, noted that the SCI research field has reached an unprecedented level of maturity as clinical trials are coming to fruition. The field is no longer focused solely on discovery but on drug development. It’s expensive and can’t be done by academic or philanthropic institutions alone. “We’re really in a new era,” Snider said. “We are going to have to think the way industry thinks.”

Snider described Edgerton as “one of the jewels in our crown.” To be sure, Edgerton has helped shape Reeve Foundation science for many years. He has reviewed grants as a member of the Science Advisory Committee; his lab at UCLA is one of six Reeve Consortium labs; and he co-founded the NeuroRecovery Network, the Reeve program to utilize activity-based therapies for functional gains and numerous other health benefits.

Edgerton’s talk wasn’t so much about
the immediate harvest of all the promising therapies for SCI— he listed a few but they are all very much in the pre-clinical stage—as much as it was an overview of his own work. Indeed, Edgerton and an international group of colleagues are getting closer to translating some of their basic science findings to the clinic. Their fruit is tantalizingly within reach. “After 35 years I’ve seen the picture begin to emerge. In the last five years it’s emerging quicker than ever. We’re learning so much; the pieces are beginning to fit together.”

Edgerton explained to the Phoenix audience that the spinal cord itself is smart and that the sensory system, not the brain, can actually control complex activity and stepping: “There is a lot of automaticity in the spinal cord. We don’t have to think about movements, the cord knows what to do. After injury,” he said, “we just have to remind it.”

In September 2009, Edgerton’s group published a major paper showing that rats with no brain input could walk on a treadmill almost normally after training in combination with a drug (Quipazine) and epidural electrical stimulation. He described how he and his group have already begun a human study to test epidural stimulation and aggressive rehab. Edgerton was clearly excited about this. He couldn’t get into detail but was obviously very encouraged by the response of the first human subject. Activating spinal circuits without any connection from above the lesion—that’s the fruit. “Let’s assume someone figures out how to get a little supraspinal input of axons across the lesion,” Edgerton said. “Now when that happens, and that taps into the spinal cord circuitry, the results can be quite big.”

Later in the day, Robert Grossman, M.D., a neurosurgeon at The Methodist Hospital in Houston, and a member of the Foundation’s Consortium Advisory Panel, described the process of bringing therapies to clinical trial. He knows first-hand the painstaking rigors of setting up a clinical network, having time to think the way industry thinks...
ing engineered the Reeve Foundation’s North American Clinical Trials Network. NACTN’s first trial has enrolled a number of patients to test Riluzole, a drug with promise for acute SCI.

Sunday morning there were more chalk talks zeroing in on the glial scar, hand function, spinal cord circuitry and brain stimulation.

The science program of the Symposium was rounded out on Sunday with a session called “Restoration of Health and Function for Chronic Spinal Cord Injury.” This featured Susan Harkema, Ph.D., co-founder of the NeuroRecovery Network and scientist at the University of Louisville, and Hunter Peckham, Ph.D., from Case Western Reserve in Cleveland. Harkema described results from several years’ worth of treadmill training studies.

Harkema said 350 patients have participated in the NRN program, with nine in ten showing improvement in health outcomes. Peckham, a pioneer in functional electrical stimulation and neurotechnology, described a new, modular implanted system his team is testing. It will affect upper and lower extremities, especially hand function. He envisions future therapies as a combination of biology and technology.

Peter Wilderotter, President and CEO of the Reeve Foundation, summed up the weekend in Phoenix: “This was an extraordinary event, one of sharing, learning and community-building. It offered a snapshot of scientific progress in the field and a view of a not-too-distant future as new therapies come to the clinic.”

— Sam Maddox

TAKE-HOME MESSAGES FROM THE SCIENTISTS

The meeting in Phoenix was magnificent. I expected the scientific excitement, but the comments from the people living with SCI were truly illuminating and inspiring. My only regret is that the meeting was not longer, so that I could learn more from people dealing with SCI pain and the other challenges that make their resilience so impressive.

_Terry Walters, Ph.D., University of Texas Medical Branch, Galveston_

It was my first time at a Christopher Reeve Foundation meeting and it was overall a wonderful experience. As a basic researcher in the field of axon growth and guidance, I seldom come in direct contact with caretakers and people dealing with SCI (or other neural diseases for that matter). It was important for me to hear their experiences and share a venue with them. It was also a great way to see the advances in treatment and translational research.

_Martin Riccomagno, Ph.D., Johns Hopkins University, Department of Neuroscience_

I am well-laden with new ideas. I particularly enjoyed the chalk talks which allowed me to learn a lot about topics I do not follow as well as I should, and ask more questions than I would normally in a traditional talk.

_Phil Horner, Ph.D., Center on Human Development and Disability, University of Washington, Seattle_

I am a person with an SCI who also does SCI research, and so I may have a little different perspective than others who attended the meeting. As a scientist, I got a lot out of being able to talk to my peers one-on-one and I’m looking forward to some new experiments that will come out of those chats. What I forget is that I’m not alone, but part of a remarkably cohesive and active community. This meeting is big enough to remind me of the scope of our community and small enough to feel an intimate part of it. If SCI research is to produce a cure (in whole or in part), meetings like this will make it possible — for science to discover it, medicine to translate it, and patients to understand it so they can push and advocate for it.

_Douglas Benson, Ph.D., Baylor College of Dentistry_
Chitosan Guidance Channels Containing a Scaffold and Seeded Spinal Cord-Derived Neural Stem/Progenitor Cells, and Chondroitinase-ABC for Repair of Chronic Spinal Cord Injury

Charles H. Tator, M.D., Ph.D., The Toronto Western Hospital Research Institute; 2-year Grant

Hypothesis: functional recovery after chronic spinal cord injury can be achieved by the combined action of chitosan guidance channels with scaffolds containing neural stem/progenitor cells and chondroitinase-ABC.

This project examines an innovative, four-part combination of treatments to repair the injured spinal cord in the chronic stage (in humans, more than 6-12 months after SCI; in rats, more than 4 weeks after injury). The strategy starts with a transplanted chitosan guidance channel inserted directly into the cavity in the spinal cord in the thoracic region 4 weeks after clip injury (which causes impact and compression similar to a human injury). Chitosan is a naturally occurring material that is well-tolerated by the spinal cord. The channel, 6 mm long and about 1.5 mm in diameter, allows nerve fibers to enter its ends and grow along its course without any inflammation or blockage by cells that can obstruct growth.

Dr. Tator’s lab is targeting regeneration of the long fibers from the brain that are responsible for movement of the arms and legs. Combined with the channel are spinal-cord-derived neural stem cells that can generate daughter cells called progenitors; these cells should help guide fiber growth in and out of the channels. Also included are supporting cells called oligodendrocytes that make the insulation (myelin) on the nerve fibers. The channels also contain a scaffold made of a fibrin substance that can increase stem cell survival after transplantation.

Finally, chondroitinase-ABC is injected at the ends of the channels; this is an enzyme that dissolves inhibitory chemicals that accumulate at the injury site. None of these selected therapies has been thoroughly evaluated in chronic SCI, individually or collectively.

Dr. Tator says his team will be able to tell if the combo treatment is successful by counting the number of transplanted cells that survive and the number of axons that grow into the channels; they will also assess the ability of the rats to move their legs.

Ephrin Inhibition of Regeneration after Spinal Cord Injury
M. Douglas Benson, Ph.D., Baylor College of Dentistry; 2-year Grant

Hypothesis: A molecule called ephrin-B3 contributes to the inhibition of axonal regeneration in the adult spinal cord; blockade of this molecule will improve regeneration after SCI.

Surviving nerve fibers (axons) in the area of spinal cord injury retain some built-in ability to grow. Axons cannot fully regenerate, though, because they are inhibited by spinal cord myelin, disrupted and distributed in the lesion area. Several specific proteins in myelin have been identified as inhibitors of axonal growth; removing any one of them in animal models results in slight or no regeneration. Therefore, a combination of therapies against multiple inhibitors is needed to increase recovery.

Dr. Benson hopes to better understand the contributions of the individual components of myelin that restrict regeneration, and thereby target them with therapies. He was on a team that discovered that one of these proteins, ephrin-B3, is a major inhibitor of axon growth in culture. The funded project aims to 1) characterize the contribution of ephrin-B3 to myelin inhibition of axonal regeneration in SCI; and 2) establish an anti-ephrin therapy to promote axon regeneration. Dr. Benson will first examine regeneration in mice that lack one or more of the known myelin inhibitors (including ephrin-B3) to compare their relative roles in suppressing axon growth. He will then compare the effect of an ephrin blocking protein, EphA4/Fc, in improving regeneration to that of blockers for other inhibitors, including the anti-Nogo antibody, which has been proven to increase axon sprouting and recovery in rats and primates.

This work is innovative, Dr. Benson said, because it examines multiple axon inhibitors simultaneously and combines multiple anti-inhibitor treatments to improve functional outcome. “Our results provide evidence that molecules with known repellent activity toward specific axon types during embryonic development maintain inhibitory activity in the adult mouse spinal cord,” said Dr. Benson. “This implies that the regeneration of different cell populations involved in SCI may each be subject to unique combinations of inhibitory molecules.

BENSON: UNIQUELY FOCUSED ON SCI

Douglas Benson always wanted to be a scientist, probably headed for a career in astrophysics. But when he was 20 he was hit by a car while on a bicycle, injuring his spinal cord. This refocused his career path toward neuroscience. He went on to get a Ph.D. at Michigan and landed a post-doc position in the Luis Parada lab at the University of Texas Southwestern. Parada was at that time a member of the Reeve International Research Consortium on Spinal Cord Injury; Benson became an Associate within the Consortium and worked out some of the basics of his current work with axon inhibition. He published a well-cited paper in 2005 on Ephrin-B-3, a potent axon blocker. Benson now has his own lab within the Baylor College of Dentistry, in Dallas.

“The plan,” said Benson, “has been to make a scientific contribution so people like me wouldn’t have to be like me.”

Benson is married and has a five-year-old daughter.

Electrical Stimulation with and without Behavioral Training to Strengthen Spared Corticospinal Circuits and Promote Recovery after Dorsal Column Lesion
Hypothesis: Electrical stimulation boosts injury-induced sprouting in spared corticospinal axons, allowing improved behavioral recovery; this recovery can be further augmented with behavioral training.

Spinal cord injury causes paralysis when the brain loses connections to the spinal cord; most people with SCI, however, have some spared connections between the brain and spinal cord. Dr. Carmel’s intention is to restore function by strengthening those spared connections using electrical stimulation.

Previously, he showed that electrical stimulation restored movement in the impaired limbs of a rat after an injury to one side of the brain. In this experiment, he uses a rat SCI model that has lost 95 percent of its brain-to-spinal cord connections. By electrically stimulating the few remaining connections, Dr. Carmel hopes to strengthen them within the spinal cord and thereby restore movement. In addition, Dr. Carmel will combine the electrical stimulation with behavioral training to maximize recovery.

The new connections will be traced using a new viral technique: First, a virus is weakened so it can infect cells but not cause illness. Then, the virus is loaded with a marker gene that is turned on by infected neurons. As the virus and the marker move from neuron to neuron, long chains of neurons can be mapped.

Knowing which specific connections are important for restoring movement will help to optimize treatments for paralysis. Dr. Carmel notes that new techniques allow non-invasive electrical stimulation of the brain. “If our treatment proves effective,” he said, “it could be brought quickly to clinical trial.”

Determinants of Outcomes from Traumatic Spinal Cord Injury: Development of a Novel Classification System to Facilitate Clinical Trials and Improved Therapeutic Strategies
Jefferson R. Wilson, M.D., The University of Toronto; 2-year Grant

Hypothesis: in traumatic SCI, it is possible to predict functional and neurologic recovery at one year post-injury; the project will create a more accurate “real world” predictive scale for acute SCI. The project will also develop an improved classification system for specific subgroups of SCI patients; this will facilitate more precise protocols for clinical trials or therapies.

Dr. Wilson, a neurosurgeon, has treated many new spinal cord injuries. “In the acute period after SCI,” he said, “the picture is murky – there are a lot of things going on that make it difficult to perform an accurate neurological exam or to make a reliable prediction for outcome.” The picture gets more clear at 72 hours but at that point certain treatment options may no longer be appropriate.

Therefore, Dr. Wilson and his group have set out to create a new classification system, taking into account neurological status as well as demographic detail, plus imaging data (MRI, CT or X-ray). “If we look at all these factors we will be able to stratify patients into more homogenous clinical subgroups, which allows us then to look into the future and assess which patients are likely to benefit from a specific new therapy – be it medication or surgery,” Dr. Wilson hopes to arrive at a practical predictive scale, along the lines of the Glasgow Coma Scale, widely used to assess traumatic brain injury. “This would be a tool every clinician could use to make better predictions of outcome.”

To create the SCI scale, Dr. Wilson’s group will comb over data obtained from 650 people with SCI in the North American Clinical Trial Network (NACTN) and the Surgical Treatment of Acute Spinal Cord Injury Study (STASCIS) databases. These databases include a rigorous analysis of mechanism of injury, demographic information, clinical findings, radiologic detail and treatment history. In addition, comprehensive outcome measurements are available up to 12 months post injury; this will establish a realistic correlation between acute injury features and long-term outcome.

“Until now, we did not have access to this level of detail about acute spinal cord injury. These measures will really improve our predictive capacity,” said Dr. Wilson.
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