

Progress in Research

BOARD VICE CHAIR ARNOLD SNIDER: THE INVESTOR'S EYE

Arnold H. Snider had no connection to the world of spinal cord injury before joining the board of directors of the Reeve Foundation. What he did have, as a veteran of Wall Street for 35 years, was a deep understanding of scientific research investment and an appreciation for strategic problem solving.

"I spent my whole career looking at health care from an investment point of view," said Snider. "I am not a scientist or physician but I had a lot of experience looking at innovation and how it affects markets and companies."

Snider also had experience in nonprofit health research. He and his wife Katherine founded Rheuminations, Inc, a charity that supports research to develop treatments for lupus, a chronic autoimmune disease.

"I'd been retired about three years from running a hedge fund," said Snider. "One of my partners on the fund was on the Reeve Foundation board; basically, he recruited me."

That partner was James O. Welch, Jr. He saw a good fit. "Personally," said Welch, "Arnie and I had a very successful financial relationship. I found him to be an exceptionally capable executive with remarkable people skills. I arranged a lunch in New York to introduce him to Dana Reeve and several key members of the board. We discussed our mission, our success to date and the enormous opportunity for even greater progress towards finding a cure in the years ahead."

Snider jumped in, ascended a steep learning curve and now, as a Vice Chair

of the board, heads the research planning subcommittee.

He has added tremendously to the board, said Reeve Foundation Executive VP for Research Susan Howley. "His experience with lupus has been invaluable. He appreciates the difficulties inher-



Sam Maddox

ent in setting up research networks and he has a real understanding of changing the Lone Ranger culture that oftentimes prevails at the bench. Moreover, his counsel to the Foundation is also informed by the realities of the marketplace. The board and our donors can have a comfort

level that Arnie has the knowledge and perspective to insure Reeve Foundation funds are wisely invested."

Welch concurs: "Arnie's decision to join our board is probably my greatest contribution to the Reeve Foundation."

Snider recently visited with Reeve Foundation staffer Sam Maddox to discuss the Reeve science portfolio, the strategy for using stem cells as research tools, and of the great potential ahead.

Q. When you came on the board five years ago, was the state of spinal cord research different than you expected?

A. I did come with some biases. One, I expected to find that the spinal cord field was not as well organized as it is. I came to appreciate that Reeve is probably the only foundation that really tries to address every facet of the problem, from biology to surgery to rehab. It's unique in that respect.

The patient population is more complicated than I appreciated initially. Spinal cord injury isn't homogeneous; it's myriad 'diseases,' if you will, depending on the timing, level and kind of injury. Plus there is the whole panoply of secondary effects related to trauma.

Third, I thought it was premature to build a clinical trial network ahead of any real drugs to test. I have changed my

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MICHAEL FEHLINGS: THE PHYSICIAN AS SCIENTIST

“There’s a big difference between hard to do and impossible.” So said Michael Fehlings, a physician who also does science, and who has done his part to stoke the flames of hope for people with spinal cord injuries.

Fehlings’ grandfather steered him toward “an honorable pursuit,” one that would “make a difference.” He chose medicine. “I knew I wanted to be a surgeon,” said Fehlings, “and early on I had an interest in the neurosciences because of the complexity of the brain, so neurosurgery seemed like a good combination.”

At the University of Toronto, Fehlings had no idea he would have anything to do with spinal cord injury or spine surgery. A mentorship with Dr. Charles Tator – a doctor who did research – exposed him to young people who had spinal trauma. “At first I had little interest in research. But my surgeon-scientist mentor showed me ways to model trauma so one could study it and approach it with an eye toward treatment. To be candid, I felt a

sense of frustration that as a physician I couldn’t do more to help.”

Out of that frustration has come a lifelong commitment to the field of spinal cord injury and paralysis, including key roles within the Reeve Foundation science program. Fehlings’ large body of research has been funded in part by the Foundation. Moreover, Fehlings is a member of the Science Advisory Council, is a key advisor to the NeuroRecovery Network and is a principal investigator in the Foundation’s North American Clinical Trials Network (NACTN). Dr. Fehlings’ research on acute SCI underpins the first NACTN trial, testing the neuroprotective drug riluzole.

“Dr. Fehlings is an absolutely essential part of our science mission,” said Susan Howley, Executive VP for Research, “because he has that relatively rare perspective of the M.D., Ph.D. His clinical experiences influence his work at the research bench and it’s important that the clinical realities of SCI are married to the

basic science. For this reason alone, his contributions to the Foundation and to the field are significant.”

(Dr. Tator, too, plays a major role at the Foundation; he sits on the Consortium Advisory Panel, which helps guide the International Research Consortium on Spinal Cord Injury.)

Fehlings has helped reshape the outlook of the neurosurgeon toward spinal cord paralysis. When he came into the profession in the early 1990s he said it was “marked by nihilism. There were people committed to spinal cord injury but the focus was more on do no harm, with a reluctance to operate and an avoidance of intervention. We put people in bed for a long time and the focus was on rehabilitation to adjust to the injury. As doctors we were telling these kids there wasn’t a lot to be done.”

Surgical techniques came along, however, to change the outlook in emergency management. Fehlings asked the questions, what if the spinal cord could be

decompressed early after injury, what if the unstable spine could be reconstructed right away. Would this facilitate better recovery? With Tator, Fehlings began to see in animals that early decompression (surgical removal of spinal bone fragments impinging the cord, done soon after injury) improved recovery. It was a struggle to validate the finding so a clinical trial was initiated; they indeed got data to support a more aggressive approach.

The multi-center Surgical Treatment of Acute Spinal Cord Injury Study (STASCIS) showed that 24 percent of patients who received decompressive surgery within 24 hours of their injury had a significant (2-grade or greater) improvement on the American Spinal Injury Association (ASIA) scale compared with 4 percent of those in the delayed-treatment group. When Fehlings presented that data last year to colleagues at the American Association of Neurological Surgeons, he noted, "It is still not a home run and far from a cure, but what it means is that 1 in 5 individuals is walking away from an injury they wouldn't normally walk away from."

"In a nutshell, we have shown that at least for cervical injuries, early decompression and stabilization are safe and feasible and appear to improve neurological outcome. The validation has been gratifying." Indeed the shift, said Fehlings, has been dramatic. Fehlings' group recently polled 1000 neurosurgeons and spine surgeons

about their attitude toward early decompression. "Overwhelmingly, the attitude now is to decompress and to do it early."

Surgical technique is only part of the shift in optimism among neurosurgeons. Drugs and therapies are coming to trial soon. What this means, said Fehlings, is that spinal cord injury may be treatable. "It may never be curable but now we can look at the possibility that effective treatments can limit disability and improve quality of life, as we salvage as good an outcome as we can."

The first treatments will focus on acute SCI, which is understandable, said Fehlings. "Initially, research studies will focus on acute injuries; this is what we can address with what we know. The big challenge is to solve the riddle of chronic paralysis. It's a tough problem." The next few years, however, will witness significant developments. "Chronic spinal cord injury is really the central focus of my lab. I see this as the big question that needs to be solved."

Fehlings believes restoring the circuitry of the damaged spinal cord will require a combination of approaches. "It won't be just drugs or stem cells or some bioengineered solution."

Fehlings lab is addressing the notion that nerve regeneration will require some sort of scaffolding. "One way to make a bridge is to inject nanofibers into the area of disrupted spinal cord. They self-organize to create a latticework. We are also using

absorbable materials that encuff the cord and provide a reparative environment.

"We're going to need more than that though: We need a source of cells. One day we may harness the stem cells in the nervous system. These cells exist but are not available in sufficient quantity. We need an exogenous source. One of the areas of biggest promise is induced pluripotent stem cells (iPS). The discovery of these in just the past few years has been one of the big breakthroughs in the field. You have the potential to take one of your own cells, say a skin fibroblast, introduce key molecules called transcription factors and turn the skin cell into an iPS cell, which resembles an embryonic stem cell. You can take that iPS cell and make a nerve cell out of it."

Fehlings noted that numerous labs are working with other cell types, including olfactory ensheathing glia, Schwann cells and adult neural cells. "The cool thing," said Fehlings, "is that these cell types are all about to go to clinical trial or are in late-stage preclinical development. I see great hope for people with chronic spinal cord injury."

"One of the important messages the Reeve Foundation needs to convey is that this research is going to make an impact. Not only for spinal cord injury but for other disorders. We may be able to apply knowledge to traumatic brain injury, stroke, even developmental conditions such as cerebral palsy."

Fehlings and Christopher Reeve met on several occasions. "Reeve was a pretty determined individual. And very inspirational. When he was on the podium, he was just magnetic. Reeve had a huge impact raising awareness of spinal cord injury. He inspired a lot of scientists and clinicians to think about SCI. It was very gratifying to see someone raise awareness and work to increase funding to make it happen. He is very much missed."

Reeve was known to push hard on the research community. "Oh, he had impatience. He wanted things to move forward; he didn't like to hear the word no. He did not like to hear that things could not be done."

Some scientists were put off by Reeve's challenge to move forward with more focus and speed. Not Fehlings. "I was like him in that way: I also don't want to hear that things can't be done. I am a person who likes to try to find the solutions."

THE 70-HOUR SHIFT: NOT WORK, PASSION

Dr. Fehlings sees patients, teaches students, runs a busy lab and manages numerous professional obligations. He joined the neurosurgical staff at the Toronto Western Hospital in 1992. He is currently Professor in the Department of Surgery, full member of the Institute of Medical Sciences School of Graduate Studies, Director of the Spinal Program at the Toronto Western Hospital, Director of the Neural and Sensory Sciences Program at the University Health Network and Krembil Chair in Neural Repair and Regeneration. His main clinical interests are in spinal neurosurgery, and his research focus is in molecular mechanisms underlying spinal cord injury.

Overcommitted? Fehlings laughs. "It's all a very good fit for me. He says 60 or 70-hour workweeks don't feel like work – it's my passion.

"I've tried to balance work, life and family by carving out times when I can focus on leisure or family." He has two daughters in college and a son in high school. The family enjoys their cottage in the Lake District north of Toronto, they take an annual ski trip and Fehlings often brings them along on business trips – they all visited South America last summer as dad lectured to scientists in Buenos Aires.

Next Step



Sam Maddox

NEXTSTEP FITNESS: COMMUNITY-BASED RECOVERY

In the fitness world Janne Kouri is what they call an animal... a regular gym rat. He's got an ironman work ethic and a routine so relentless it puts many a serious athlete to shame. Kouri's not just training, though. He's recovering. Before: total paralysis. Now: walking with a walker.

Kouri puts himself through the paces at a facility he and his family created, NextStep Fitness near Los Angeles. The gym is a community-based facility in the Reeve Foundation's NeuroRecovery Network (NRN), the innovative activity-based rehab program designed to maximize health and function after paralysis.

The NextStep logo is a long and winding road that ends in sunshine. Perfect for a sunny SoCal disposition and a perfect metaphor for Kouri's own life story.

Kouri, born in Sweden and raised in New York, broke his neck in 2006 diving into the Pacific and hitting an unseen sandbar. He was a young, buff guy, a former college football player and erstwhile ski bum. He and his then-fiancée Susan Moffat checked out his rehab options –

all over California, in Denver, Atlanta, Chicago and beyond. They weren't hearing the word recovery. Said Kouri, "I wanted to go to a proactive, progressive place, not one where you just learn how to live your life in a wheelchair."

Through a friend they heard about Frazier Rehab Institute in Louisville, the lead center in the NeuroRecovery Network, ground zero for locomotor training. The head of Frazier's rehab research department, Susan Harkema, urged Kouri to come to Louisville to become the first inpatient in the NRN. "She was the only one who gave us hope," he said. "She said 'we'll push him, get him up on the treadmill.'"

The couple flew from L.A. to Louisville as soon as Kouri's medical complications (respiratory and skin infections) cleared up. He stayed in Kentucky for a year: half the time as an inpatient, half on his own continuing aggressive rehab — working and stimulating his body.

The treadmill work didn't start out great: Kouri passed out after 11 seconds. He made it to 30 seconds the next time,

and after a week could stay on his feet for extended periods. "After about four months of five days a week training, I was able to wiggle my big toe," he said. "But the more immediate results were better muscle tone, cardiovascular health and improved blood pressure." There's also a mental part of locomotor training: "Simply put, it felt great to stand up and 'walk' again."

When it was time to move back to California, Kouri could move his arms again and maneuver himself in a wheelchair but he wanted to continue the aggressive therapy. He and Susan soon discovered that there were no locomotor training sites on the West Coast. If they wanted it they'd have to build it.

With encouragement from Harkema and the NRN, Kouri opened NextStep Fitness, operating as a nonprofit. NextStep was the first NRN facility that's not in an academic or medical center setting (a second will open its doors shortly in Chicago). "We put together a business plan and with friends and family raised about \$1 million." Staff has been fully

trained by NRN experts. The NRN protocol at the academic centers includes only incomplete injuries but this is not the case for the community-based facilities. “We absolutely have seen progress with the completes,” Kouri said. “It may not be leg movement but in terms of muscle mass and tone, cardio-fitness, strength in the core areas, everybody benefits.”

NextStep is a gym, but it’s become a quasi rehab too. Said Kouri, “One mistake I made initially was to assume that the majority of NextStep clients would use it they way people use a Gold’s Gym or Bally’s – come in, pay a monthly fee and work out. We found that the majority of our clients hadn’t seen any rehab. Zero rehab. From day one we have almost morphed beyond the fitness center model.” The difference between the routine at this place and the mainstream is all about the R word. Recovery.

“In many rehab settings they say, ok, your arms work. Let’s get you to brush your teeth. What we say,” said Kouri, “is, ok, your arms work, fine, let’s get to work on what isn’t working. Let’s get as much back as we can.”

NextStep opened in the South Bay-L.A. town of Lawndale in June of 2008. A few weeks later Janne and Susan were

married. NextStep is booked up full. Kouri and the NRN want to take the model and expand it. The only limiting factor is money. “We want to bring the idea of lifetime wellness into many communities,” said Kouri. “People should not have to travel long distances or move their families to get needed exercise.”

People should also be able to afford to be fit. The NextStep model is built on that concept. “We offer services at a fraction of what it costs us. A client may pay \$135 an hour here; it runs us \$340 an hour for the four staff people who work with each client on the locomotor training. We operate at a loss: \$400,000 this year.”

The gap? NextStep is partially supported annually by the Reeve Foundation through the NeuroRecovery Network. What’s left is made up for by fundraising. Friends in New York and Chicago have helped. They are also looking at grants and collaborations, and for corporate support. A scholarship program is in the works to make sure clients get the therapy they need, regardless of financial situation.

One question that remains is, what about getting reimbursement for a NextStep workout? Why don’t insurance companies pay? Kouri said one client at NextStep did get it covered by private

insurance. A large segment of the industry is unconvinced of the value of hardcore rehab. He has a message for the insurance industry: Activity-based rehab works; the concept is evidence-based. “If companies don’t pay for therapy on the front end, it will cost a lot more down the road for all the complications of paralysis.”

What’s next for Kouri? “My goal is to keep going and going. Who knows where this will take me? I would love to walk but it’s not just about that. I want to live as healthy a life as I can. In spinal cord injury, there are all sorts of secondary conditions – if you don’t exercise you’re at greater risk.”

NRN DATA: WHAT IS KNOWN SO FAR

Results of NeuroRecovery Network activity-based interventions and locomotor training will be published soon. What is known is that treadmill training is good for everyone. Here are the highlights of the data:

- ▶ Recovery can occur years after injury
- ▶ Over 300 people have received locomotor training in the NRN, over 275 in clinical centers, and over 25 in fitness facilities
- ▶ The majority of individuals experience improvements in function
- ▶ Many have improved their overall health
- ▶ Intensity of training and weight-bearing are important
- ▶ Developing new measures of recovery not based on compensation has improved understanding
- ▶ Individuals receive standardized treatment across NRN sites
- ▶ It’s spreading: centers teach standardized activity-based interventions to others in their region

Source: S. Harkema, University of Louisville/NRN



Sam Maddox



Sam Maddox

EDGERTON: SPINAL CONTROLLED, FULL-WEIGHT WALKING

For the first time, rats with completely severed spinal cords were able to walk bipedally on a treadmill with a near normal gait while bearing their full weight. This research, funded in part by the Reeve Foundation, showed that the walking was facilitated not by restoring brain control but by tapping into circuitry in the spinal cord itself.

The work, published in the journal *Nature Neuroscience*, comes from a collaboration of scientists in Switzerland, Russia and the United States. The project was led by Reggie Edgerton, Ph.D., professor of physiological sciences and neurobiology at the University of California, Los Angeles, and a member of the Reeve International Research Consortium on Spinal Cord Injury.

To achieve what is being hailed a breakthrough in research to treat spinal cord injury, completely paralyzed rats received a combination of a drug to induce a serotonin-like effect and thus facilitate synaptic transmission, epidural

electrical stimulation of the spinal cord, and aggressive rehabilitation (treadmill) training.

The animals began to walk within a week after treatment; after two months each could walk for half an hour on the treadmill bearing full weight. The rats could step sideways, backwards and could vary their speed. The researchers suggest that the drug and electrical stimuli prepare the neural circuits for activation, and that active training completes the process.

“What this demonstrates,” said Edgerton, “is that in the rat, there are neural circuits within the lumbar-sacral spinal cord that can control full weight-bearing and coordinated stepping without any input from the brain. But the more novel result is that these experiments show that the sensory system can actually control the stepping.”

While the experiment is based on a tripart treatment, it’s the ability to tap into sensory circuits that is of primary importance, said Edgerton. “We’re seeing these

results because we have figured out a way to get to this circuitry – the spinal cord already knows what to do, it just needs to be reminded what to do. And it needs to be prepared, physiologically; the way we prepare it is pharmacologically and with epidural stimulation. That’s our way of saying, OK cord circuitry, get ready for this information. This sensory information is going to come through and you’ll know what to do with it.”

“Another thing that’s unique about this paper – and people have not grasped the importance of this – is that the sensory information coming from the lower legs when one steps is going back to the spinal cord and is being interpreted almost as well as you would expect the brain to interpret it.”

Said Edgerton, “We usually think of sensory information as being a mechanism for correcting an action, for adjusting movement when we make a mistake – when we trip, for example. This research tells us that spinal circuitry is really a

much more sophisticated system, it's not just a reflex system, it's predictive of what should be happening. Based on the information that it has just received, it's already predicting what should happen next. It's generally been thought of as a feedback system. But it's really what engineers refer to as a feed-forward system."

Edgerton said that for example, we don't usually think about the act of walking. It's more or less automatic. "We're not always thinking, well, what did my leg just do and what's it going to do next to walk. I think these results demonstrate that automaticity is basically located within the spinal cord."

Edgerton accepts that this study is indeed a "breakthrough," although for a scientist who's been on the locomotion path since the early 1980s, he keeps it in perspective. "These ideas have been evolving for a long time. They started in the late 70s, early 80s. And so where our thinking is now is the result of cumulative studies over years. Many people have helped contribute to the idea – as many scientists say, we're constantly building on everybody else's ideas. Of course many of the ideas have come from our lab; we've been going in this direction a long time." Said Edgerton, "One of the reasons we've been able to make progress is the key contribution [on epidural stimulation] from our Russian colleagues at the Pavlov Institute in St. Petersburg."

"So I'm thinking, why is this being considered a big breakthrough? I'm seeing it as incremental. But I'm OK considering it a breakthrough because it really demonstrates that full weight-bearing walking can be achieved with a combination of specific interventions, all of which scientifically make sense, so it's by putting all these pieces together we've reached a significant point."

When the media get hold of the word 'breakthrough' it usually implies a direct link to human treatment. To be sure, the abstract from the published paper (from first author Gregoire Courtine, who was a post-doc in the UCLA lab for five years before heading last year to the University of Zurich) states: "These findings provide a strategy by which individuals with spinal cord injuries could regain substantial levels of motor control."

But Edgerton, who prefers to let the facts speak, again urges perspective. "Certainly we scientists are obligated to do

whatever we can to explain the results of our experiments. Sometimes even if you explain the results as they are, though, they're going to be interpreted in a number of ways and some are going to say 'well that's expressing false hope.'"

Others will expect human therapies right away. "These experiments have been freely interpreted as being the same as what one should do in humans... forgetting about the difference between rats and humans," said Edgerton.

But the scientist can't control the headlines in newspapers. "We need to tell everybody what these results are, very straightforward; we don't have to make

them more than they are or less than they are. But if we didn't think these experiments were related or had any significance to our progression toward human treatments, we wouldn't be doing them. So, to imply that it has something to do with humans is OK with me. How much one wants to extend and generalize that and convert it to hope isn't something that's under my control."

G Courtine, Y P Gerasimenko, R van den Brand, A Yew, P Musienko, H Zhong, B Song, Y Ao, R Ichyama, I Lavrov, R R Roy, M V Sofroniew & V R Edgerton, Transformation of nonfunctional spinal circuits into functional states after the loss of brain input, Nature Neurosci (2009) September 20; doi:10.1038/nn.2401

WHAT'S NEXT FOR THE EDGERTON LAB?

Biology:

Edgerton and his team continue to study the hidden potential of neural networks within in the spinal cord. They believe the cord is smart and that the same biochemical phenomena that accompany learning in the brain also occur in the cord.

Pharmacology:

"We're not doing anything in humans yet," said Edgerton, "but that's another obvious direction to go. It's a very important part of the puzzle." Edgerton speculates that a drug to stimulate nerve function could be applied intrathecally. "Conventional technology exists to have pumps implanted to apply the drug baclofen on the spinal cord to treat spasticity. That anesthetizes the spinal cord, and obviously that's not what we're interested in doing; we're interested in just the opposite. We can imagine our group finding, or someone finding, an optimal pharmacological cocktail that could be placed in a pump to facilitate the locomotion."

Neuroprosthesis:

Said Gregoire Courtine, first author of the *Nature Neuroscience* study: "The idea is to develop a neuroprosthesis for the spinal cord, basically a set of electrodes that can be implanted below a lesion to stimulate and activate the circuits." This might enable a completely paralyzed person to stand, maintain balance and execute some effective stepping. "They're not going to be stepping normally, but small improvements can be made in an individual's life."

Human Recruitment:

"We have plans to implant our first sub-

ject with conventional epidural electrodes very soon," said Edgerton. The type of stimulators used with the rats are similar to what is already used in people with spinal cord injuries. "The electrodes for humans appear to be safe. In fact, they are already being used conventionally – for spasticity and pain. No one has used them for locomotion before, although three or four years ago a group from Phoenix implanted epidural stimulators in an individual with an incomplete injury who had some ability to walk; when stimulated, that subject felt he could walk with more ease."



Gregoire Courtine

Add Regeneration?

There is plenty to speculate about here. Said Edgerton, "We're doing these experiments assuming there is no axonal connection above and below the spinal cord lesion; we're seeing what activating spinal circuits can do without any connection. But assume that someday someone is going to figure out how to get axons across the lesion. Now when that happens, if that connection can tap into the smart spinal cord circuitry we're talking about, the results can be quite big."

NEW INDIVIDUAL RESEARCH GRANTS

Thalamic mechanisms of central pain.

Funded for two years, total \$150,000.

Principal investigator, Asaf Keller, Ph.D., University of Maryland

Spinal cord damage often results in chronic, debilitating pain. As many as 80 percent of people with spinal cord injuries develop steady, unrelenting central pain syndromes (CPS); these are highly resistant to medications or surgery.

Research from the Keller lab has identified a critical pathway in the brain that plays a major role in the development of central pain. Using a unique rodent model, he discovered a malfunction in a normally pain-blocking area of the brain known as the zona incerta (ZI). This is in turn related to altered activity in the thalamus, a key brain region for processing sensory information.



Asaf Keller

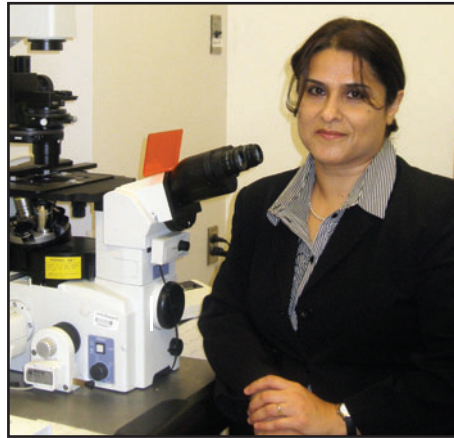
only certain pain information to be experienced by the brain; the ZI filters or inhibits the pain information that passes to the thalamus. In the current project, spinal cord injured animals with CPS show reduced inhibition from the ZI, and abnormally high activity in the thalamus. This unrestricted flow of sensory information causes pain.

Pain information travels from the limbs through the spinal cord to the brain. Keller has previously shown that under normal conditions, the zona incerta allows

only certain pain information to be experienced by the brain; the ZI filters or inhibits the pain information that passes to the thalamus. In the current project, spinal cord injured animals with CPS show reduced inhibition from the ZI, and abnormally high activity in the thalamus. This unrestricted flow of sensory information causes pain.

There may be ways to modify the zona incerta so it inhibits pain as it should. Keller's lab has shown that, after SCI, the ZI gradually stops working over a period of several weeks. He and his colleagues hope to find a way to intervene during that time to keep the zona incerta active. Drug therapies are a possibility. "We're also considering options such as non-invasive brain stimulation, stem cell implants or even occupational therapy — exercises patients could do to stimulate the zona incerta," Keller says.

"We're hopeful we'll find relief for these patients, at last."



Soheila Karimi

A combinatorial strategy to optimize neural repair and plasticity after chronic spinal cord injury.

Funded for two years, \$149,494 total. Principal investigator, Soheila Karimi, Ph.D., Toronto Western Hospital Research Institute

"Considering the substantial number of paraplegic individuals who sustain lifetime disabilities," said scientist Soheila Karimi, "new therapies need to be developed to facilitate repair and regeneration of the chronically injured spinal cord."

Karimi's lab proposes to attack chronic SCI with a four-part combination: transplantation of adult neural stem cells to replace lost neural cells; promotion of neural stem cell survival and differentiation into oligodendrocytes using a growth factor cocktail; using the enzyme chondroitinase ABC to block the inhibitory components of the glial scar; and lastly, intensive rehabilitation therapy to stimulate the activity-dependent repair of spinal cord circuits.

"The discovery of neural stem cells in adult central nervous system has offered tremendous hope for new treatments for SCI," said Karimi. Recent findings from her team have shown that a strategy using these neural stem cells, along with growth factors, has potential for the repair of injured spinal cord. But using neural stem cells remains a challenge, mainly due to the inhibitory properties of the scar tissue surrounding the lesion site.

"Based on our preliminary findings, we anticipate that our combined therapeutic strategy would have a significant impact on the outcome of neural stem cell transplantation in the chronically injured

spinal cord. The experiments proposed here could represent a major advance in the application of regenerative medicine to the treatment of patients with chronic SCI," she said.

"People ask, is there hope. I tell them, we're working hard; there are many promising results and I believe there is good reason for hope. But it's a very long road to get there."

Modulation and activation of excitatory spinal interneurons necessary for walking movements.

Funded for two years, \$150,000; principal investigator, Martyn D. Goulding, Ph.D., The Salk Institute for Biological Studies, La Jolla, CA

Interneurons in the spinal cord play a key role in generating the complex patterns of muscle activity that enable us to walk. These interneurons, together with motor neurons, form a neural network known as the central pattern generator (CPG). The CPG is able to function independently of the brain to generate the coordinated and rhythmic firing of motor neurons needed for walking.

Goulding's lab has studied the function of many of the cell types in the CPG, including a class of excitatory neurons that connect with motor neurons. These cells, the V3 interneurons, are important for maintaining the overall excitability of the locomotor network.

Goulding found that removing V3 cells from motor circuits in the spinal cord causes a loss of organized "walking" activity. This has led to the working hypothesis that enhanced V3 neuronal activity is important to maintain ambulation.

Goulding, therefore, proposes to see whether certain drugs known to modify locomotor activity in the spinal cord can directly activate V3 cells. He further plans to test whether V3 interneurons are direct targets of descending pathways that are already known to activate the CPG. Said Goulding, "These studies will help us devise new therapies and approaches that are aimed at activating V3 interneurons and the locomotor network in the injured spinal cord," and therefore improved walking ability.

For more on individual grants, see www.christopherreeve.org/research

NEW MEASURES TO DETECT TREATMENT OUTCOMES

The Reeve Foundation's Neurological Outcomes Assessments (NOA) Task Force, an integral part of the North American Clinical Trials Network (NACTN), has begun the much-needed work to develop, test and validate improved outcome measures for use in human clinical trials of spinal cord injury.

"Clinical trials and therapies for SCI are being implemented and may be doomed to fail without appropriate outcome measures to demonstrate that the successes in animals can be translated to humans," said NACTN Principal Investigator Robert G. Grossman, M.D. "Our goal is to develop sensitive outcome measures for SCI and to expedite their use clinically."

Grossman added that in the long-term, treatments will probably come in a series, "including therapies directed at neuroprotection, glial scar, modulation of nervous system, regenerative therapy, plasticity therapy and so on. No single approach is likely to have dramatic effects."

The most common outcome assessment tool for SCI in use today is the ASIA Impairment Scale (AIS, from the doctors' group, American Spinal Injury Association). But this test, which measures neurological level of injury, was never meant to be used as an outcome measurement. It's not sensitive enough.

"Manual muscle testing in the AIS likely won't detect small changes that occur after a therapy," said Susan

Harkema, Ph.D., from the University of Louisville and co-chair of the Task Force. Many of the therapies headed for clinical trial won't result in something as easy to spot as say, walking. "The worst thing that could happen is that an intervention could be successful and not show up on the measurement scales we have now."

Said Susan Howley, Reeve Foundation Executive VP, Research: "NOA is an extremely important initiative of the Foundation. We need reliable and sensitive measures that can detect small, incremental changes in patients."

The 25-member NOA group, representing experts from Europe, Canada and the United States, has met twice in recent months. The group agreed to pursue two categories of outcome instruments:

- those with the potential to be ready for use in clinical trials in 2010, and
- those that will take longer to develop and validate but have strong potential for accuracy and reliability.

The Task Force also agreed upon broad outcome areas: autonomic function (including measurement of changes in bowel, bladder and sexual function), motor function, pain and sensory response, and quality of life (meaningful changes reported by the patient).

Development of new tools to measure outcomes is a key part of the process. The NOA panel considered, for example, devices to better measure hand strength. "We need good hand function testing,"

said Harkema. "The AIS doesn't give us a lot of information regarding hand function." One hand-test possibility is a device called GRASSP (Graded Redefined Assessment of Strength, Sensibility, and Prehension), developed by scientists at the Universities of Toronto and Zurich, and partly funded by the Reeve Foundation. Another is QMAD (Quantitative Motor Assessment Device) from the Grossman group in Houston.

Several other ways to assess outcome are being considered, including the use of evoked potentials, myometry (measuring muscle tone), by using video recording over time, and by keeping track of autonomic progression (blood, bowel, bladder and sexual changes) Also, asking the patients the right kinds of questions can help assure better outcome assessment.



Sam Maddox

l to r, 1st row: Jill Wecht, Andrei Krassioukov, Susan Harkema, Naomi Kleitman, Susan Howley. 2nd row: James Guest, Anthony Burns, Stephen Burns, Amie Jackson, Tania Lam, Peter Ellaway, Milos Popovic, Zev Rymer, Molly Verrier, Robert Grossman. back row: Graham Creasy, Martin Schubert, Arthur Prochazka, Art Sherwood, Ken Curley, Tim Boone, Bernard Conway



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SNIDER ON INVESTMENT. . .

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mind on that.

Also, I was skeptical about the Consortium and the efforts to encourage collaboration. With my background in the lupus area I was skeptical you could ever get academics to work together. But the Reeve Consortium, in the almost 15 years it has operated, has been probably the best example of collaboration amongst academics that I know of. I think everyone in the SCI field realizes no single lab has enough firepower to make a real difference.

The Consortium is an extraordinary group of people with valuable long-term chemistries. You go to their meetings and it hits you: How else could you ever discover treatments for spinal cord injury unless you get people like this together?

Q. The Consortium is one part; the individual grants program is another. What balance does the board seek?

A. I'd like to see a fairly even portfolio between the Consortium and grants to individual investigators. This where the out-of-the-box type thinking occurs. We encourage investigators with bright ideas with seed money that may lead to greater support from NIH down the road. But the value of the grants program is only as good as the peer review it gets. You can waste a whole lot of money quickly if you don't have the best people in the field reviewing applications. Really, if people are looking to give money, they should look closely at who is on the science review committee.

Q. You never met Christopher Reeve and had no link to SCI. What motivated you?

A. What hooked me personally was seeing paralyzed individuals, often injured as a result of a traumatic accident. Their minds are perfectly intact, but they are trapped in bodies that don't function the way they should. In my view it's just one of the most horrendous things that can happen to a person.

And you look at the spinal cord...the lesion is such a relatively small space. The peripheral nervous system can repair itself but the brain and spinal cord cannot. In all the experiments over the years, no one has been able to get the axons to cross the scar and grow to the other side of the space. But in our day and age, repair ought to be so simple. That was

part of what turned me on. There just has to be a way to do this.

Q. You said you changed your mind about the North American Clinical Trials Network. Why is that?

A. NACTN is important to test new drugs but it's more than that – NACTN is in fact establishing a continuum of care

“People want stem cell therapies to happen in the short term but it's not, in our judgment going to happen.”

in acute spinal cord injury. First, the surgeons in the NACTN group are establishing the surgical standards of care – early decompression and stabilization. The NACTN group is also developing a data registry of acutely injured patients so we can chart the normal course of recovery, something we don't even understand at this point in time. What this means is that eventually, if a person gets the right surgery, plus the right therapies, and then goes on to get the right rehab – this person has a chance to get back to a reasonably functional state.

Q. A strategy for early intervention?

A. It would be nice if we could cure spinal cord injury by regenerating the lost nerve cells, but we all know that's going to be a long haul. Speaking for myself, I would like to see the Foundation put a lot of emphasis on surgical interventions and getting people into the right rehab programs. What the data clearly show is that intense rehab is good for everybody. No matter what stage they are at.

Of course there are a lot more people with chronic SCI and we must remember them. Those injured more recently may still have a lot of hope we'll find something. Those many years post-injury probably don't look at recovery the same way. The real thing people who've been paralyzed a long time worry about is how they can best manage the aging process. They've learned how to deal with being paralyzed, the day-to-day stuff. But they ask, what will aging mean to my health and function? The Foundation is plan-

ning to explore issues of aging with SCI. We need to focus on helping people with autonomic problems, with bowel and bladder issues, and pain. These are such a big part of living with paralysis. By design, we must allocate funding to strategically address these health and quality of life challenges.

Q. The NeuroRecovery Network has had some success with older injuries...

A. If you look at what the Foundation has accomplished, the value of aggressive rehabilitation has to be at the top of the list. It's the crown jewel – people should have a lot of hope about it. We've got something now that will get people back to a more reasonable standard of living. With the data coming out of the NRN, activity-based recovery and locomotor training should be the standard of care.

Q. What is the Reeve Foundation stem cell strategy going forward?

A. The Reeve Foundation is already known for its support of stem cell research. While so many focus on transplanting stem cells, we wanted to know what we could do now to best facilitate the use of stem cells in injury and repair. Frankly, I'm not hugely optimistic about using stem cell transplants for SCI therapy in the short run. Putting one cell, or group of stem cells, into the lesion area is not going to do much. There are so many types of cells disrupted by trauma. Stem cell treatments will likely require immune suppression. Timing will be an issue, as will infectious complications. So much remains unknown about these cells and their capacity for repair, but also their potential to do harm.

We decided to develop stem cells as a research tool. We now have the ability to grow human stem cells in a straightforward way – we can make all sorts of neuronal cells. It's an unlimited process.

This technique has the potential to dramatically change the field of preclinical research in spinal cord injury. It allows the research community to move beyond animal models only as the basis of preclinical research. We are dealing with real human cells and it is now possible to use these cells in ways that could not have been imagined not long ago. One could put motor neurons in a dish with muscle cells and study how connections are formed. Or cut an axon and study in real-

time the physical and biochemical changes. Combinations of neuronal cells may be developed as assays against which it is possible to screen therapeutic molecules. The possibilities are almost infinite, and the good news is that this technology is here now. We don't have to wait for long-term studies or lengthy regulatory processes. An orchestrated program using some of these novel approaches is now underway in our Research Consortium, lead by Rusty Gage and Sam Pfaff, both at The Salk Institute.

Q. So people may need to adjust their expectations about stem cells

A. I am not bearish on the transplantation technology. I see this avenue of research as a 10 to 15 year pursuit.

So many parents, spouses, friends of those who are newly injured are frantic to find the state-of-the-art for their loved ones. You find, though, that the state-of-the-art is not as far along as you had hoped it would be. That's a realization most people come to after a while, and it's a hard one to accept.

Q. Some people are not going to wait; they're going abroad for stem cells...

A. In my view going overseas is highly dangerous, and it's highly likely that these off-shore interventions are not going to work. The technology is not far enough along to have much confidence in it. For people who just had an injury, psychologically it must be so overwhelming. We are totally sympathetic to the desperation that loved ones must feel in this situation and, for that reason, the Reeve Foundation feels an extreme sense of urgency to get to effective therapies as soon as possible.

Special Thanks

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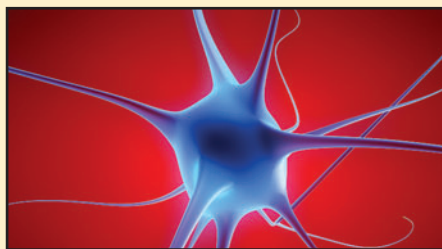
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