Recently, the European Journal of Neuroscience (EJN) selected its Best Publication Award for 2013, honoring a paper, “Combined delivery of Nogo-A antibody, Neurotrophin-3 and NMDA-NR2D subunits establishes a functional detour in the hemi-sected spinal cord,” published by lead author Lisa Schnell from the Martin Schwab lab in Zurich, working in collaboration with Victor Arvanian, then a researcher at the Lorne Mendell lab at the State University of New York, Stony Brook. Both labs are members of the Reeve International Research Consortium on Spinal Cord Injury.

In this joint effort, the authors found that treatment of paralyzed animals with anti-Nogo-A (to overcome myelin inhibition), in combination with genetically induced expression of Neurotrophin-3 (NT-3, to enhance nerve growth) and boosting a glutamate receptor subunit (to increase synaptic plasticity), created a functional “detour” around the injury site. This improved recovery of function in adult rats.

Schnell and Arvanian accepted the award at a ceremony in Prague. Below, Schnell describes the combination study, and her career.

I began my career as a hematologist and then I joined the Martin Schwab lab in Zurich where we worked exclusively on the spinal cord, trying to find a treatment. The long-held dogma was that injury to the spinal cord cannot be repaired, that the central nervous system, as opposed to the peripheral nervous system, has no ability to repair itself. This might be attributed to lack of trophic or growth-promoting factors. Schwab found there is an inhibitory protein that prevents growth. This was quite novel; nobody had thought of this before. There has been a long history of this specific protein, analyzing it, and even giving it a name – Nogo-A. It is now very well known. Once we had the protein we could make

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antibodies in our lab; we applied them to cell cultures, to frozen sections, and finally to rats in the lab. To our joy – not to our surprise because we had hoped for it – the result was really clear that fibers could now grow when we applied the antibody to the injured spinal cord. While blocking this molecule allowed regeneration — functional repair could be shown for the first time in adult rats and monkeys after spinal cord injury, thus overturning the longstanding dogma — the growth was in a few fibers. It was not as massive as we had hoped. We thought success was right around the corner but it was not there. It was long years away. We had to look for other means to enhance the amount of fiber growth in the spinal cord.

Because our result was so novel and so important, a whole community of researchers came in to the field to look for other molecules that are needed, or other inhibitors that had to be shut down. More molecules have been found, which makes the problem very complex, perhaps even hopeless. With so many molecules, how will we ever find what promotes nerve fiber growth? The best thing might be to find a key molecule, one that switches all the others on or off on demand. The other way is a combinatorial approach with different molecules used together.

The paper that won the EJN award came to be thanks to the Reeve Foundation Consortium, a network of experts in the field of spinal cord injury who sit down together and discuss their newest research results. [The Martin Schwab lab has been a member since the very beginning, in 1995.] Consortium member Lorne Mendell was talking to me about his latest finding – that a magnesium-based block that is responsible for nerve conduction could be reversed by adding a juvenile form of the NMDA receptor, together with a growth factor called Neurotrophin-3. This combination would enhance synaptic plasticity.

Lorne was very thrilled about this, but at the same time, disappointed. If one looked at older spinal cord injuries in rats, it didn’t work there. I said to him, of course not, because you did not use the Nogo-A antibody. Well, this clicked. Lorne said, why don’t we put our expertise together and do a really sophisticated experiment. Naive as we were, we thought we could do this experiment quickly. But actually, it was a long way to go. Any kind of combination treatment needs so many controls. In our case, with three active components you end up with eight groups of rats, each group with 10 to 12 animals. That is a huge study.

Martin Schwab was very helpful. He allowed me to fly to the U.S. and Victor Arvanian, from the Mendell group, came over to our lab to help with operations and fiber counts.

Animals were trained before surgery to specific behavioral tasks. The animals all received a hemisection injury – partially paralyzing them. Once the animals recovered from surgery, they were again trained to specific tasks. In seven or eight weeks half of animals were shipped back to Victor’s lab for in vivo [live] electrophysiology studies. The other half remained in Zurich to look at the histology of the spinal cord. It took us a long time. Some groups had to be repeated to get the optimal numbers.

What we found was that the combination of three ingredients, the NMDA receptor subunit, the addition of Neurotrophin-3 and of course the antibody to Nogo-A – the combination showed better outcomes in behavior. It was quite clear from the electrophysiology measurements that these animals used...
Paul Lu is a prominent spinal cord injury scientist at the Center for Neural Repair at the University of California, San Diego, and VA San Diego Healthcare System. He has serious skin in the game: his own spinal cord injury motivates him toward finding cures, this despite the fact he was trained to study plants, not animals. “I hope to solve the mysteries of spinal cord repair, for all of medicine, and also for myself,” said Lu. “I have always had faith that science could restore a meaningful degree of my lost function.

Lu remains faithful: He was lead author of a 2012 Cell paper that showed unprecedented growth of axons above and below a complete lesion in spinal cord injured animals, using stem cells as a bridge and a complex cocktail of molecules to spark growth. The recovery of function was modest but the regeneration was meaningful. Work continues as Lu fine-tunes the combination of ingredients and moves the model to primates, and he hopes not too far off, humans, including those with long-standing injuries.

Paul Lu didn’t choose neuroscience; it more or less chose him. “I came to the U.S. in 1990 to study plant biology at UC Davis. I had been a teacher in my native China but things were opening up for young people back then – closed doors were suddenly opened, and my country sent me to the U.S.”

After getting his Ph.D. at UC Davis, Lu stayed there for a post-doctoral fellowship. All was going according to plan until a 1996 car accident on a Christmas trip to Las Vegas injured Lu’s spinal cord. Lu was married and had a son, and no health benefits.

Lu wanted to stay in academia but was discouraged that he could not stay on full time at UC Davis. He was about ready to give up. “I had my ticket and was all set to go back to China; my brothers would have taken care of me.”

Just days before Lu’s plane reservation to China, he visited the Resource for Independent Living Center in Sacramento, 20 minutes up the road. “I met the director and told her, ‘I need a job, any job.’ The director said, ‘Can you type?’ Of course, I told her, I’m a Ph.D. She hired me for a social work job, which I learned quickly to do, and for a few months I helped other people with disabilities find work and housing. Being able to work and knowing I could work was really important in regaining my confidence.”

Lu never considered social work as a career. He was a trained scientist and wanted to re-enter the field. He began to wonder about the science of the spinal cord. “I looked at the literature to see who was doing SCI research. There was the Miami Project, the Fred Gage lab in San Diego, and the Mark Tuszynski lab, also in San Diego. I wrote to them, told them I have the Ph.D. in biology and that I’d like to be involved in SCI research. I didn’t hear from them. But one day, Dr. Mark
Rob Summers was the first one. He had been hit by a car and had a C7-T1 spinal cord injury. He came from Portland, OR to Louisville, KY with no motor function below his chest. Researchers there, led by Susan Harkema, Ph.D., implanted an epidural stimulator over his lumbar spinal cord. That, plus a lot of aggressive Locomotor (treadmill) Training, enabled him to stand on his own, take steps and after seven months, to the surprise of the research teams at the University of Louisville and UCLA, regain voluntary motor function when the stim was on. Even more surprising, Summers regained bladder control and near normal sexual function, even when the stim was off.

Lead scientist Reggie Edgerton, Ph.D., of UCLA: “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, by the 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.”

Summers was what researchers call an “N of one,” that is, a single case study – interesting but statistically weak. Would the same procedure work in others? The answer is an unqualified yes. Four young men have now gotten epidural stimulators and Locomotor Training. Here, in brief, are their results, in their own words:

**ROB SUMMERS.** On the third day in the clinic after the surgery, they said, ‘Let’s just see how it goes to stand.’ They put me in a harness over the treadmill, my weight suspended 100 percent. They lowered it down and down until I’m standing, full weight-bearing. It was just an incredible feeling. I hadn’t moved anything in four years. My legs were supporting me. There was nothing to help me balance. I could feel my legs working, I could feel my feet under me on the treadmill. At first I didn’t comprehend the significance, but I soon realized what an incredible thing this was. It was like a giant weight was lifted off my shoulders. I had worked so hard for so long, and to be standing for 15, 30 seconds, it was so emotional for me in many ways.

After seven months we found out that while the stimulator was on, I was able to voluntarily control my toes, ankles, knees and hips, on command. This was something that was completely unexpected.

There were other benefits, too. One day I realized I could sweat again, and regulate my temperature, feel hot and cold. I could also feel light touch. I regained control of my bladder, bowel and sexual function and my circulation improved. I’m not 100 percent but the changes really impact my quality of life. I’m happy to have been part of the experiment and be able to help the scientists streamline their techniques. After seven months I could take steps; Dustin, patient number four, could step in the first week. I joke with [lead researcher]
Susie Harkema, “by the time you get to patient number 1000, they will be running out of the lab in five days.”

If I were to address a person with a new injury I would say without a doubt, this will change the quality of your life. We are not quite there yet, but cures are just around the corner if we continue the research efforts and experimental trials.

Kent Stephenson. Mt. Pleasant, TX. On June 9, 2009, I was practicing and getting ready for my summer motocross racing season, which started the following week. But everything changed that day. Going off the face of an 80-foot tabletop jump, the motor on my dirt bike locked up, causing me to crash. I did several cartwheels and in my landing broke T5 and T6 in my back. I was paralyzed from the chest down – T4 Asia A.

I went to Craig Hospital in Denver for my inpatient rehab and came home from there in August. I was home for a week, then went to Frazier Rehab in Louisville, KY to start Locomotor Training and therapy. I did the [Reeve Foundation] NeuroRecovery Network training and community fitness program for a year at Frazier before I became aware of the epidural stimulation research, which of course was being done right there. I went through the screening and was selected.

The first time they turned the stim on I felt a charge in my back. I was told to try pull my left leg back, something I had tried without success many times before. So I called it out loud, ‘left leg up.’ I felt a sort of charge go down my leg and then a tightness. This time it worked! My leg pulled back toward me. I was in shock; my mom was in the room and was in tears. Words can’t describe the feeling that overcame me at that moment – an overwhelming happiness. I had been told by doctors that because I was an ASIA A I would never be able to move voluntarily. The feeling is amazing. It really gives you back that part of yourself you feel you lost when you became injured.

When this all started, my injury was supposed to be a life-ending deal, really, that is how the doctors told it to me. But in fact, it has been an adventure. Being a part of the stim program has really changed my life and enables me to do all the things I used to do, like deer and duck hunting, going off-roading, running heavy machinery at work, everyday 9-5.

I wasn’t 100 percent sure I wanted to give up two years of my life to go through the training and everything. But it has totally been worth it. I got a fortune cookie recently after my injury. It said, “Everything’s impossible until somebody does it.” I still have that note in my wallet, and always recite it in my head when I’m trying new things.

Andrew Meas. Louisville, KY. I broke my neck seven years ago. It was dusk, I was cruising about 35 miles an hour on my motorcycle. I got hit head-on by a car. I flew 100 feet almost to the other side of the highway; I did a superman dive, landed on my head. I broke my neck at C6-7. After complications with pneumonia – I almost died while on the breathing machine – I was weaned and eventually transferred to Frazier Rehab, where I stayed for three months. Of course, I heard about Locomotor Training right away, it’s done right here. I participated, but my insurance only paid for two weeks. I was put into the lottery, I guess you’d call it, for the research program there.

Once I was picked, they had me do 80 sessions of Locomotor Training, to make sure I had no motor function below the lesion level. I did not.

I got the surgery and waited a few weeks. Once the stim was turned on, I could stand on my own. It was amazing. I forgot how tall I was. It was very emotional to be standing after sitting in the chair for so long. Then, on command I was able to lift up my legs – pretty easily, even without the stim. I can’t describe it, it was just incredible.

Yes, leg function is a spectacular feature of epidural stimulation but for me the most important benefit is in managing my autonomous dysreflexia [AD, a dangerous blood pressure reflex for people with injuries above T6]. Before the stim, I could sense when my bladder was full. If I waited too long to empty it, though, I would get a pounding headache, a sign of AD, and a painful reminder that this could lead to stroke. Now, I can hold my bladder longer and have no AD symptoms. Bowel function has improved a little bit. As far as sexual function goes, that has improved greatly – everything is possible now, and there is no AD.

Dustin Shillcox. I was in a car accident on August 26, 2010, on the interstate near Green River, WY. I was driving a work vehicle when the tire blew out and the vehicle rolled. I was ejected from the car and paralyzed at level T-5, ASIA A. A few months after being discharged from the hospital, I saw a news report that researchers had for the first time enabled a paralyzed person to stand on his own. Once I found out about Rob Summers, I called and had my name put in the pool so I might have a chance to be a part of the study. The following summer I got the call. I packed my car and headed for Louisville.

The feeling I get when I turn the stim on is amazing; when I stand or work on walking I feel great because I’m doing things that I was told would never happen again. The ability to move my legs is awesome and it makes me excited for the future because the four of us in the epidural stim program all keep making progress. I have also had progress in improved bowel, bladder, and sexual function – this alone has given me a strong self-confidence. The stimulator makes me feel normal. It’s like I’m back. If I talk with someone who has a new spinal cord injury I’d tell him or her about how exciting the research is and how important it is to stay healthy and keep involved with therapy. I tell people – and show them by my example – that scientists are making great improvements for people with a spinal cord injury.
Tuszynski was in Davis to perform some surgeries. He called me, asked if I had time to meet. I told him my story; he said, ‘You deserve a chance to work.’ So he offered me a post-doc position at UCSD.”

Dr. Tuszynski recalls their first contact: “I remember receiving an email from a man at UC Davis who had his Ph.D. in plant molecular biology. He said he had recently sustained a spinal cord injury, and would like to volunteer to be a research subject or to do research. But since I visited Davis frequently, and this was a fellow scientist who was in need, I owed him the respect and decency to at least meet with him. But the man I met, Paul Lu, was startlingly intelligent, dignified, and accomplished. Although I did not really have sufficient funding at that time to hire him, I did anyway, taking a chance that both he and the funding would work out. It was one of the best decisions I have made. Paul is an exceptional individual and human being, before one takes his injury into account. After taking his injury into account, he is even more impressive.”

Lu already had expertise in molecular biology and histology. It did not take him long to get up to speed on the basic biology of spinal cord trauma. He devoted himself to the Tuszynski lab; his first publication there showed how to clone the important axon growth factor BDNF, leading to an experimental gene therapy to promote motor axonal regeneration after spinal cord injury.

Lu hadn’t been in San Diego long before Tuszynski published a paper that generated high publicity, and high hopes. “Mark’s initial strategies for enhancing regeneration after SCI focused on delivery of growth-promoting factors to lesion sites. In 1997 he had a paper in the Journal of Neuroscience; it got a lot of attention, even in Chinese newspapers. Mark had used gene therapy to promote axon growth – he used a genetically modified
fibroblast, a skin cell, to express a growth factor called NT-3. When grafted into the spinal cord, there was significant functional recovery. This was exciting for the field. At the time, I thought we were really close to the solution. However, delivery of NT-3 promotes corticospinal tract axonal growth around the lesion site and not through (or into) the lesion site; also, this experiment used an incomplete dorsal hemisection model that does not occur in human spinal cord injury. But now, here we are 16 years later, we know we still have a way to go.”

The Tuszynski group tried other ways to promote growth. In 2003, Lu was co-author of a study that grafted NT-3 in a large chronic SCI model. Grafted animals showed significant growth of corticospinal axons up to 15 mm beyond the lesion site and showed a modest but significant improvement in locomotor scores, compared to control-grafted animals. The next year, the lab tried the neurotrophic factor NT-3 combined with a molecule called cAMP, which activates nerve cell signaling. This time, axons regenerated not only into the cell graft that was expressing NT-3, but also beyond the injury site, more than after treatment with cAMP or NT-3 alone. Lu and his colleagues believed this to be a major advance in strategies to enhance spinal cord repair. “We observed, in our own hands for the first time, convincing evidence of axonal bridging in mid-cervical spinal cord lesion sites.” Nice result, but still not ready to be a treatment.

In 2007, Lu and Tuszynski tried to coax their growing axons to cross the tough scar tissue that surrounds the lesion site of chronically injured animals. They grafted bone marrow stromal cells (MSCs) into mid-cervical SCI sites of adult rats, six weeks post-injury; this provided a hospitable environment for axons across the scar. Other animals received MSCs genetically modified to express Neurotrophin-3 (NT-3), which further stimulated axon growth.

Meanwhile, Lu had become interested in the potential of stem cells. “Cell lines were becoming available to study. I asked Mark if we could pursue this area. He wasn’t convinced. ‘You can try,’ he told me. So starting in 2002 or so I began to graft embryonic spinal cord derived stem cells in the spinal cord. The trouble was, they did not stay in the lesion area. They died.” Lu said he tried to graft an immortalized stem cell line that survived in the lesion site but was not able to fully differentiate into mature neurons. “My challenge was, how do I get the real stem cells to survive in the spinal cord injury site?”

The answer, Lu would learn, is in a cocktail approach, a combination of stem cell transplantation and a unique blend of ten growth factors imbedded in a sticky fibrin paste. The work was detailed in 2012 in Cell.

“We broadened our perspective considerably by adopting combinatorial approaches. We were recently successful bridging transected spinal cord with neural stem cells that extend axons into host spinal cord and form connections, or synapses, with nerve targets beyond the lesion. This regeneration can be achieved even in a chronic injury, even after substantial delays from the original injury, even after three months in rodent models.”

The study was widely reported.
Henry George Stifel Jr., 1927-2013

Henry George Stifel Jr., known as Hank to his friends and colleagues, died on Sept. 18, 2013.

The ancient Egyptians believed that a damaged spinal cord could not be repaired. It would take centuries and a powerful combination of scientific curiosity, serendipity and a small band of warriors whose lives intersected with spinal cord injury to change that dogma.

Hank Stifel was one of the earliest of those warriors. After his son Henry injured his spinal cord in 1982, the Stifel Paralysis Research Foundation was born. Hank and his wife Charlotte believed that if they could support the best research out there, eventually treatments would come. But the truth was that back then, there was precious little spinal cord research to support.

In the mid-80s, Hank learned of the American Paralysis Association, which was doing the same thing as the Stifel Foundation, only better. APA used independent scientists to advise its board on research investments. In short order, Hank joined the APA board, became its chair and eventually moved APA from Dallas to New Jersey. And when Christopher Reeve was at Kessler Institute after his accident, it was Hank Stifel who reached out to him and Dana and began their initiation into his world of research. And so it was that what began as the Stifel Foundation in 1982 (literally on a card table in a second-floor bedroom of the Stifel home) emerged in 1999 as the Reeve Foundation.

If Hank knew one thing, it was that the spinal cord is a dauntingly complex tissue and no one person alone, no one lab, no one set of expertise, would be able to fix it. He asked Carl Cotman, a prominent Alzheimers’ investigator, to create a panel of scientific experts to vet research for APA and make funding recommendations to the board – and more specifically, he asked Carl to tap his own top-tier colleagues to join. Hank encouraged the pioneering work of Swiss scientist Martin Schwab. First funded by APA in the late 1980s, Schwab is funded today by Reeve – his is one of seven laboratories in the International Research Consortium on Spinal Cord Injury. The 1995 launch of the Consortium, the first of its kind in spinal cord research, was a direct outcome of Hank’s belief in the power of collaboration.

So much of what the spinal cord field is today grew out of Hank’s belief that if the best science was funded, there would be cures. The work is unfinished but the Reeve Foundation commitment to his vision is stronger than ever. We will finish what he began.

Rest in peace, Hank.