Consortium Symposium: Moving from Lab to Clinic

Spinal Cord Injury: Translation-al Approaches to Mechanistic Studies, a two-day gathering held at the Salk Institute in La Jolla, CA, brought together top international researchers in the field.

Will Reeve, right, opened the symposium by challenging the research community to keep future beneficiaries of their work in mind: “Your work has a practical application for real people; they are not data points or numbers. They are people living with paralysis who have hopes and dreams. Just as my dad did. So I urge you, work faster, work better, and work smarter. The community needs you.” See full coverage page 2.

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The Reeve Foundation sponsored a major scientific symposium in February: Spinal Cord Injury: Translational Approaches to Mechanistic Studies. The two-day gathering, held at the Salk Institute in La Jolla, CA, brought together top international researchers in the field. Sixteen presentations covered a range of topics including clinical trials, technological approaches to functional recovery, and discoveries of molecular pathways that may lead to new therapies for spinal cord dysfunction.

The symposium was sandwiched between a Reeve Board of Directors meeting and a meeting of the seven-lab Reeve International Research Consortium on Spinal Injury.

The symposium was opened by Salk scientist Sam Pfaff, who co-organized it with James Fawcett, from University of Cambridge in the U.K. The Pfaff and Fawcett labs are members of the Reeve Consortium.

Pfaff introduced Elizabeth Blackburn, Salk President and 1984 Nobel Laureate (she discovered telomeres, important end-segments of chromosomes). She welcomed the attendees and urged the scientists to remain “unflaggingly persistent” in their work. “Go beyond what is believed to be true,” said Blackburn.

Foundation Board Member Will Reeve then offered greetings, reminding this prominent segment of the research community how much people with SCI are counting on them. “My realm is the human side,” said Reeve. “Your work has a practical application for real people; they are not data points or numbers. They are people living with paralysis who have hopes and dreams. Just as my dad did. So I urge you, work faster, work better and work smarter. The community needs you.”

Fawcett chaired the first scientific session, “Bringing Therapies to the Clinic.” He noted that a doctor friend disparaged the field of neuroscience for having progressed so very little in the 100 years since Spanish scientist Santiago Ramón y Cajal characterized brain and spinal cord anatomy. “We really ought to have done better,” Fawcett conceded.

Fawcett introduced Aileen Anderson, also a member of the Reeve Consortium. She described how her work, at the University of California, Irvine, went from animal research to human clinical trials. She and her science partner (and husband) Brian Cummings developed animal models for using fetal-derived neural stem cells, first in thoracic injuries, then in people with cervical injuries. The thoracic data showed some sensory improvement in patients; the cervical data showed some sensory and motor recovery, but not enough to justify continuing the trial. StemCells, Inc. closed the trial down in May 2016.

But there’s more to the story. Anderson and Cummings, using the StemCells, Inc. proprietary cell line, were unable to show
that they worked in preclinical cervical animal models. They warned the company but the trial went ahead anyway. Anderson and Cummings have since published two journal articles about the failed trial, posing important questions for the SCI field regarding animal studies, cell potency, and technical aspects of cell transplantation. They also raise key questions regarding the ethics of informed consent for patients in stem cell trials. For more on Anderson and the Stem Cells, Inc. trial, see page 8.

Martin Schwab, from the University of Zurich, was up next. He’s also a Consortium member, and well-known for his work to neutralize chemical barriers to regeneration. His antibody to a specific inhibitory molecule in the spinal cord (anti-NOGO) has been tested in rats, and now monkeys. “The monkeys treated with the anti-NOGO antibody recovered function in their hands, very well.” What surprised him, Schwab noted, was that animals regained bladder function. He suggests the antibody encourages compensatory growth of spared spinal circuits; the spinal cord appears to adjust to this new growth on its own.

Meanwhile, human studies are progressing. A 52-patient clinical trial is set for European SCI centers in coming months. Reggie Edgerton, a scientist from UCLA and a former member of the Consortium, presented data on a spinal cord stimulation device his lab is developing. By stimulating spinal cord interneuron circuits, the device enables motor recovery in animal models, and to a limited extent, human subjects. The process is similar to epidural stimulation, which involves implanting a stimulator over the dura of the spinal cord. The transcutaneous device requires no surgery.

Transcutaneous stimulation works for most patients on the first try; half are able to initiate standing with one session, Edgerton reported. He can’t fully explain why spinal cord stimulation works but his data indicates that the spinal cord is able to learn and adapt, and thus switch on automatic programs built into the cord. “There has to be some level of neural reorganization, we just don’t yet know what it is. We are able to get a signal across the lesion with a bit of stimulation. There’s a synergistic reorganization occurring. The brain can figure out how to connect itself to spinal cord circuitry.”

More testing is coming, Edgerton said, including integration of spinal cord stimulation with other technologies (cell therapies, drugs, robotic devices and nerve transfers). “We don’t know how far we can go with this, but there is tremendous plasticity in the spinal cord. Right now the science is two or three years ahead of getting it to patients.”

Sam Pfaff introduced Phil Popovich, a researcher at Ohio State. Popovich said his focus is on a new way of seeing spinal cord injury, studying its impact on the entire body. “Spinal cord injury is a systemic disease,” he said. Injury to the cord affects what Popovich termed the three super-systems in the body – the nervous system, the immune system, and the gut.

For example, SCI has a profound impact on the spleen and on the liver. A weakened spleen leads to immune suppression. The post-SCI liver accumulates fat and becomes diseased, and is less able to modulate inflammation. It may be possible, said Popovich, to improve the health of both spleen and liver and thus affect the nervous system, and recovery from trauma.

The digestive tract, the microbiome of “bugs” in the gut, is also wracked by SCI. This creates a dysbiosis, said Popovich. But in animal experiments, gut health was restored using a strong probiotic; this “normalized the effect of SCI on the gut,” spared tissue and improved function. In a recent set of experiments using a novel sterile surgical technique on germ free mice, transplants of healthy fecal matter into the animals boosted their immune function and “normalized their physiology.”

In a section of the program called Devices and Technology, Richard Anderson, a researcher at Caltech, described his work with neuroprosthetics. His team implanted a 96-channel sensor in the brain of a quadriplegic subject. They used a real-time imaging technique to position the sensor in the location in the man’s brain for intent to move. After much training and tuning of the equipment, the subject could modulate individual neurons in his cortex; in time he could modulate 30 neurons, enough to move a prosthetic arm in three dimensions with only his thoughts. “Eric’s goal,” said Anderson, “was to drink a beer, moving the robot arm to grasp the glass and bring it to his mouth.” Anderson showed a video of the subject doing just that.

Anderson reported that another subject implanted with the sensor could type with
her group uses intraspinal implants of fine wires to target motor regions of the spinal cord. Experimental animals recovered over-ground walking ability, including speed and distance. “Engaging the spinal networks is an effective means for improving mobility after spinal cord injury,” said Mushawar. She reported that a combination of cervical stimulation and lumbar stimulation was better than lumbar alone.

Chet Moritz, from the University of Washington, and a member of the Reeve Consortium, reported on his work with neural devices to promote recovery. Recently, his lab tested Edgerton’s transcutaneous spinal cord stimulator on a patient with impaired hand function as a result of a C3-C4 injury. After one series of stimulations, the patient demonstrated up to eight times more strength in thumb pinch. “All measures of grasp were improved,” said Moritz, who showed a video of the subject being able to feed himself.

Zhigang He began the third segment of the symposium, Molecular, Cellular and Circuit Pathways. He is a pioneer in the concept of repowering nerve cells to mount a regenerative effect. He found that deleting a gene called PTEN enables nerve fibers (axons) to grow with unprecedented vigor. Because PTEN is related to tumor suppression, though, He is looking for a more optimal way to reprogram growth in nerve cells for clinical application, perhaps by adding growth factors directly to axons. He described recent studies using growth factors IGF1, BDNF and osteopontin to promote axon regeneration and improve functional scores on a horizontal ladder test.

Mark Tuszynski from the University of California, San Diego, presented data on his lab’s neural stem cell work. Grafted cells, which are intrinsically programmed for high growth, survive transplantation into a spinal cord model and grow long distances up and down the spinal cord. Moreover, host cells regenerate into the grafts. “There is absolutely remarkable outgrowth,” said Tuszynski. “It is astonishing to see.” The grafted axons also appear to make the correct connections to the appropriate targets in host tissue, suggesting that guidance mechanisms are in place. Studies continue, including work with primates. These stem cells are not ready to translate to humans, but “this is stunning biology,” said Tuszynski. “An anatomical mechanism is established that has the potential to be a functional relay across the lesion site,” he said.

Jack Martin, from the City College of New York, introduced the term “electroceuticals.” This is the use of electricity or magnets as therapies to stimulate the brain or spinal cord toward useful functional recovery. Martin’s experimental approach uses noninvasive stimulation of the motor cortex. He showed evidence that stimulation increased nerve signals associated with regeneration, boosted sprouting and improved skilled motor recovery in chronically injured animals.

James Fawcett, known for his work to apply an enzyme called chondroitinase to degrade the barrier formed by post-injury spinal scar, described recent work in his lab to define the role of integrins in the success or failure of regeneration. Integrins are molecules that activate cell signals related to nerve growth. Integrins are inactivated by inhibitory molecules following SCI (NOGO-A and chondroitin sulfate proteoglycans).

“Would axons regenerate if they had an appropriate integrin on their surface,” he asks. Fawcett thinks the answer is yes; he is focused on two integrins, alpha9 and kindlin, that promote extensive axon growth and functional recovery in animal models. He is hoping to find the right inte-
grin to restore pelvic sensation – important for bladder and sexual function.

Jeffrey Macklis, from Harvard, studies the growing tip of an axon, called the growth cone. His work suggests that growth cones are autonomous cellular components that are far more important than previously thought. “The cones are isolated mini cellular units themselves,” he said. “The growth cone may be the place to look for what goes on in regeneration, rather than in the cell body itself.” The implications are that targeting growth cone function could lead to SCI repair strategies.

Adam Hantman, a scientist at the Howard Hughes Medical Institute Janelia Farms campus in Ashburn, VA, focused his presentation on the neural circuitry that generates skilled use of the hand. He used a mouse model to demonstrate that such skilled behavior originates in a specific part of the brain cortex. Using optogenetics to activate nerve pathways using blue light, Hantman showed that skilled reaching and grabbing depends on cortical networks, but also on a sort of brain relay, the basal pontine (BPN). Deactivating either the cortex or the BPN removes the ability of animals to achieve reaching and grasping tasks. Ultimately, Hantman hopes to fully map out how motor skills are wired in the nervous system, and to understand which parts of the circuitry are most important for specific tasks.

Next up was Frank Bradke, from the German Center for Neurodegenerative Diseases in Bonn, who presented data on a group of molecules that prevent axon regeneration. These molecules are essential during development to prevent overgrowth of nerve connections as the body first forms its nerve networks. The molecules remain in the body and are activated by injury. Bradke wants to know, is it possible to remove or block them? Turns out a common medication used to treat pain, gabapentin, binds to inhibitory molecules and neutralizes them.

Sam Pfaff and his lab group hope to better understand how spinal cord interneuron networks work, and how they might better be manipulated to improve movement after injury. Using sophisticated gene sequencing tools, the lab identified several key genes. One, called V2a, is functionally important for respiration when it’s found in the brain, and for locomotion when found in the lumbar part of the cord. Using light-activated tools (optogenetics), Pfaff said the lab showed that turning V2a off disrupted reaching ability in animal models. The goal, eventually, is to detail all genetic cues related to recovery of function in the spinal cord.

Ben Barres, from Stanford, described recent work from his lab showing how nervous system cells called astrocytes are changed by trauma from passive support cells to killer cells. The lab used an optic system model, and is now studying a spinal cord model, with the help of the Anderson lab at UC Irvine. The goal is to target the bad astrocytes and therefore promote cell survival and better recovery after SCI. For more on this study, see page 10.

The Lorne Mendell lab at Stony Brook University is a member of the Reeve Consortium. Mendell, trained as a neurophysiologist, studies neuroplasticity and has a longstanding focus on the functional effects of neurotrophins in neonatal and adult mammalian spinal cords.

Mendell wrapped up the symposium with an upbeat overview “We as a field may be able to offer significant help to patients,” he said. “There is real hope now. And we have to go further.” The work presented at this meeting, said Mendell, “leaves me feeling very optimistic.”

— Sam Maddox
After that, I was recruited to work for a small pharmaceutical company in Palo Alto, Syntex Research. I had a couple of skills they were looking for so I got a real job and a real paycheck and it was great from the standpoint of being young and having no family. The company sent me to neuroscience meetings and I saw again the spinal cord injury research community, with that same passion that I had left, and got to thinking, I would really like to get back to that. So I actually packed up after five years at Syntex. Part of it was my son had been born and I didn’t like coming home and telling him that I wasn’t sure I was doing anything really meaningful. And part of it was just missing the spinal cord injury research. I saw Brad Stokes [from Ohio State] at a neuroscience meeting and he said, ‘did you know I have an opening in my lab?’ I knew him from working with Paul back in Florida. And so, in 1995, I left. And I never looked back.

Brad brought me in as a full-time research scientist until I could get my own grant. I had been working with growth factors so he started me on projects looking at BDNF related to spinal cord injuries.

My first grant as principal investigator, which came from the Reeve Foundation, characterized axon growth in a mouse model of injury. Then I got grants to start looking at inflammation at the cellular level.

Ohio State had a pretty unique team of collaborative scientists at that time, including Mike Beattie and Jackie Bresnahan, and Brad; Phil Popovich, Dana McGtigue and Michele Basso were postdocs. We were publishing together and working together, and that was the culture at Ohio State. That culture is still there, that idea that spinal cord injury research is a little different; we’re not really going to get anywhere by competing with each other, we actually have to work together.

Why would you leave Ohio State? What attracted you to the government job?

LJ: First, there was no program director for the spinal cord portfolio. Naomi Kleitman had left to go to the Neilsen Foundation, so there was a gap that had to be filled by someone who knew about spinal cord injuries; otherwise, the position was going to be filled by someone who didn’t know the field. And that bothered me.

Part of it was timing; it was the right time in my life to move on. My son was off in college and I was becoming an empty nester; I felt like it was a good time to pack up and do something that would broaden my horizons. But I think the biggest reason was the feeling that as a bench scientist I was looking at problems that were becoming increasingly specialized and small. I was focused on fixing astrocytes, which is an important problem, no question about it. But could I spend another 15 years at the bench, looking at astrocytes? I had an opportunity to consider working those years shaping change; that was so compelling to me that I made the leap.

What does a program director do? Could you give us a job description?

LJ: Our job really is to oversee the spending of taxpayer money. What I do every day is kind of threefold. One is to be the liaison for investigators who are studying spinal cord and nerve injury research, help them to formulate their questions, help them to navigate the peer review process, to know where to send their grant, know what to do when their grant gets scored poorly. Is this a grant they just should abandon because, really, there’s nothing here? Or is it a grant that perhaps they didn’t sell in the manner they might have?

The second part is doing my public service at NINDS making sure that spinal cord injury research is on the agenda, and sticking my nose in whenever I see something that says brain and doesn’t say spinal cord, and telling my colleagues that they’re forgetting us. The third part is trying to decide what things need to be done scientifically and what things need to be left alone. That’s the hardest part because I’m not on the bench anymore so I don’t know science.
like I used to. I know it in a broader context and much less in a specific context. I go to meetings and try and listen across the spectrum, listen to the clinicians, listen to the advocates, and listen to the people with spinal cord injury, and listen to people who are succeeding in moving other fields forward and find out what they’re doing right.

So what percentage of projects that are submitted are getting funded?
LJ: Our annual appropriations budget includes 80 to 85 percent commitment to continuing, noncompeting grants. That gives us a discretionary amount for anything new of only about 15 percent of the total institute budget. At NINDS, we are funding regular project grants, for this year, only up to the 12th percentile.

Are any of these grants funding research that you would call speculative or risky?
LJ: Only the top of the top flow up to that fundable percentile. That’s one of the reasons that we fund more basic research – based on good ideas that have already been vetted to the point that we know that when we invest over a million dollars in them, it’s not likely to come back as nothing. But every innovative advance that we’ve made to date has come from good solid research. If we invest only in trying to find the shiny lead horse and translating that one across the finish line, I think that we’re going to end up in the gutter more often than not. It is, really, the role and the mission of NIH to support the ideas that are coming from fundamentally strong science.

Did you ever meet Christopher Reeve?
LJ: Yes, he was an inspiration to my generation by going lab to lab and telling the scientists they’re not doing enough.

He said that to you?
LJ: Yes. Reeve came to Dodd Hall at Ohio State and met with researchers. He went around the table and asked each one of us to talk about our research programs, and of course we had our elevator speeches handy. But for every one of us, when we told him what we were doing and why, he wanted to know why we hadn’t done more, did we know about what else was going on in the field. That was really compelling. I think it changed our complacency.

What else really changed the general outlook toward SCI research?
LJ: Realizing the difference between intrinsic and extrinsic contributors to regeneration was a big change. It was all about the environment of the injury site until probably Marie Filbin and the group at Miami and others who started saying wait a minute, it’s not that simple. The nerve cells themselves need help too. That opened a lot of doors.

Another change was when rehabilitation researchers came in and said activity is essential, we need to add it to everything, I think that was big. More recently, Reggie Edgerton [at UCLA] and Susie Harkema, [University of Louisville] confirmed that a complete injury is not complete and showed that there is at least one way to gain voluntary activity in patients with chronic motor complete injuries. That’s groundbreaking.

Another change came about after Kim Anderson’s paper (2004) ranking the needs and wishes of people living with paralysis relative to research. The community said we all have different needs – hand function for quads, for example, being much more important than walking. But that caused the research community to say, it’s not all about motor function. There’s a lot of other stuff that’s going on. That was a big deal.

How would you advise the SCI community to get involved with public science?
LJ: I think about this a lot because I don’t know the answer. I think what’s really important is that we not compete with each other so much. This problem is big enough for everybody to figure out who is best at what. And I think that it isn’t about who gets the glory, it’s about making sure all the bases are covered.

The advocacy groups and the funders must work together to create a language and story, a narrative, that makes it clear that this is a long haul process, this is a hard problem we’re trying to solve. It’s not going to be solved magically through one bullet. We’re going to build a toolkit that will be useful for a variety of things. And we’re building it together by not stepping on each other’s toes, but by figuring out who’s doing what. That’s my vision for my legacy — what can I do to encourage collaboration. Because we’re all working towards the same goal and it’s not about who funded the most exciting paper.

People are still going overseas for stem cells. What do we need to say about that?
LJ: It’s a challenge. There’s no question that stem cell tourism, avverting accepted regulatory standards to sell a therapy with false evidence, is charlatanism. There’s not a lot of solid evidence that we have any idea what stem cells or other cells can do. And yet there are at least 12 registered cell therapy clinical trials ongoing in the world and two in the U S right now. These are looking at safety, but they’re also looking for efficacy, and we don’t really know the potential

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Barres Lab: When Astrocytes Become Cellular Assassins

Astrocytes are finally getting noticed. But they’ve had to become villains to be taken seriously. These tiny star-shaped nerve cells are four times as common as neurons, the brain and spinal cord cells that conduct electro-chemical messages up and down the nervous system, and therefore get all the attention. For most of the last 100 years, astrocytes have been pretty much ignored, relegated to being bubble-wrap packing for neurons.

Now we find out that mild-mannered astrocytes have a dark side. In a study published earlier this year in the top-tier journal *Nature*, the Ben Barres lab at Stanford showed that resting astrocytes can become reactive, which turns some of them toxic. These little assassins then destroy nerve cells and are a likely cause of many neurodegenerative diseases and trauma.

The Barres lab is one of seven in the Reeve Foundation’s International Research Consortium on Spinal Cord Injury. Barres is a physician/scientist and professor of neurobiology, developmental biology, neurology and neurological sciences.

“We’ve learned astrocytes aren’t always the good guys,” said Barres, who’s studied them for three decades. “An aberrant version of them turns up in suspicious abundance in all the wrong places in brain-tissue samples from patients with brain injuries and major neurological disorders from Alzheimer’s and Parkinson’s to multiple sclerosis. The implications for treating these diseases are profound.”

Barres said the findings are “the most important discovery my lab has ever made.” Stanford postdoctoral student Shane Lidelow, Ph.D., is the study’s lead author, and is an Associate in the Reeve Consortium. He performed most of the research.

Lidelow said he began his graduate studies looking at delivering drugs beyond the protective seal of the blood-brain-barrier. “But I jumped ship. I completely switched fields because I wanted to study astrocytes. These are the most abundant cell in the brain and spinal cord. Astrocytes are intimately involved in many aspects of normal neuron development and function- ing, but their interactions and importance during injury or disease is largely unknown. They have to be doing something, just by nature of there being so many of them. And if we see these non-neuronal cells acting dysfunctionally, this becomes an exciting avenue for investigation.”

Astrocytes never got much attention, Lidelow said, because tools were not available to explore them. “Ben’s lab had previously worked out how to grow purified astrocytes in culture. The lab also published data on what genes are activated when you injure an astrocyte, including what genes change when an astrocyte takes on a reactive architecture. What was striking was that the helpful or harmful nature of reactive astrocytes depends on the injury that induced them. For instance those induced by inflammation – we do this experimentally by injecting the endotoxin lipopolysaccharide (LPS) on the surface of some bacteria – are thought to be harmful. On the other hand, astrocytes induced by ischemic stroke are more helpful. What is still a mystery is which are present following trauma such as spinal cord injury.”
Liddelow and Barres labeled the two kinds of reactive astrocytes A1, the harmful ones, and A2, the seemingly protective ones. In the new work, the lab found that three specific molecules (called cytokines) are produced when microglia (immune cells in the brain) respond to LPS-induced inflammation. These molecules cause astrocytes to produce a toxic soup that is fatal for many types of nerve cells, including cortical neurons, embryonic spinal motor neurons, and oligodendrocytes, the cells responsible for the myelin insulation on nerve cells.

They also used an optic crush model to see how A1 astrocytes behave following traumatic nerve injury. This showed that the A1 broth invaded the area of damage, and that two-thirds of the neurons died after a week of exposure.

Scientists have long known that cutting a nerve fiber (axon) in the central nervous system causes the entire neuron to die quickly, but why the whole cell dies has been a mystery. Now they know: the toxin from A1 astrocytes bathes the entire area, including the cell body.

For some reason, certain motor neurons escape the A1 assault, which leads the scientists to suspect that a specific molecule is toxic to certain CNS neurons and mature oligodendrocytes. Liddelow said the group is trying to identify this mysterious A1 kill switch. They are also working to promote the more helpful A2 state, to understand why it responds to stroke.

They are still working out the formula for the A1 toxin. Meanwhile, the Barres group has found they can use drugs to stop A1 cell formation, and thus prevent neurodegeneration and stimulate growth of nerve connections (synapses). By chemically blocking the three cytokines, the A1 astrocytes lose their sting; they no longer produce the toxins that destroy nerve cells following an optic nerve crush.

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Finding a biological culprit, and then finding a way to neutralize it, drives biomedical researchers along what Liddelow describes as the “long slog” toward clinical relevance. In this case, the fact that the cytokines can be blocked leads the research team to focus on developing new therapies to preserve nerve cells. “Acute injuries of the retina, brain, and spinal cord, and even neurodegenerative diseases, may be more treatable than we thought,” Liddelow said.

Another part of the study showed that an A1 astrocyte can be deactivated and returned to its nontoxic resting state. Liddelow speculates that the key challenge will be the specific elimination of A1 astrocytes alone, while leaving non-activated astrocytes intact.

Liddelow is completing his postdoc assignment at Stanford and is seeking to set up his own lab. Because of his deep involvement in the Reeve Consortium, he is leaning toward studies of reactive astrocytes in spinal cord injury models. “A1 astrocytes in the initial injury following SCI cause the death of neurons. And these astrocytes may also hinder the recovery and regenerative effort following SCI, therefore impeding axon regeneration and synapse formation. A1 astrocytes in both acute and chronic SCI are high on my list of projects to follow,” he said.

“If you look at the new paper, half of it is based on a trauma model. This is directly because of my interaction with the other Consortium labs and the amazing scientists like Louis Reichardt and Albert Aguayo, who were on the Consortium Advisory Panel (CAP) at the time. I got very important feedback from these colleagues – and having people like [Consortium principal investigators] Sam Pfaff (Salk) and Martin Schwab (Zurich) looking closely at our data, that was invaluable as we prepared for publication.”

Liddelow is especially grateful for having Ben Barres as a mentor. “I will always be mindful of what Ben taught me: He would say, ‘do not be afraid to rock the boat. Always question the dogma.’ He’s given me the strength and background, and the confidence to build my career on.”

Liddelow said he’s going to make sure astrocytes – good or bad – remain in the spotlight. “As I transition to my own independent lab and research program, I hope to secure funding to continue to investigate astrocyte functions in SCI – ultimately aiming to push towards more translational outcomes to benefit patients.”

—SAM MADDOX
The November 2015 press release made the company’s data sound so promising. After receiving stem cell injections in their cervical spinal cords, a small number of patients in a clinical trial called the Pathway Study reportedly regained strength in their fingers. Three quadriplegics were able to pick up a key, put it in a lock and turn it 90 degrees.

StemCells, Inc., the small California company running the trial, enthused about these preliminary anecdotes: This result, they said, would “change the trajectory of recovery following a spinal cord injury (SCI).”

Six months later, that trajectory went straight south – the company shut down the Pathway Study. Yes, StemCells said, the data were promising. But not enough to justify spending more money; the company didn’t figure to meet trial targets established with the FDA. The news shocked the spinal cord injury community. But disappointment is only part of the story. Questions have been raised about the identity and potency of the stem cells, about the trial design, and about the ethics of patient recruitment.

Two researchers involved for more than a decade in the development of StemCell’s human neural stem cell line have come forward with more reasons to be concerned. Their experiments, shared with the company, may have predicted the Pathway trial failure. The trial went forward anyway.

Aileen Anderson and Brian Cummings, wife and husband, are scientists at the University of California, Irvine (UCI). Anderson’s lab is part of the Reeve International Consortium on Spinal Cord Injury. A good part of the UCI team’s work in recent years, under contract with StemCells, tested a cell line called HuCNS-SC (human central nervous system stem cells). In 2005 UCI data showed that HuCNS-SC had a positive effect on animals with thoracic injuries. That led the company to initiate a 12-patient clinical trial in 2010, first in Switzerland and later with trial sites in Canada and the United States. The trial tested the safety of cells in people with mid-chest (thoracic) injuries. Data has yet to be published on that clinical study but the company did report at a 2015 science meeting that some of the participants recovered sensory function.

That was enough to empower StemCells to want to try its stem cell line in cervical SCI. The FDA approved the Pathway Study in June of 2014.

Anderson and Cummings expressed serious reservations about jumping to the cervical spinal cord; this presumes that cervical and thoracic injuries are similar. There are major differences, however. A cell graft in cervical cord could induce unwanted results not predicted by the thoracic experiments. For example, nerve circuits in the cervical spine are associated with autonomic function, which is closely related to blood pressure dysfunction. Moreover, higher injuries are known to suppress the immune system, which might be compounded as SCI human subjects are given drugs to prevent immune rejection of transplanted cells.

The UCI scientists shared data with StemCells showing that its research grade batch of HuCNS-SC had some effect in cervically injured animals, but that its clinical grade line not only didn’t work in the cervical model, it suggested a loss of function in the animals.

StemCells dosed the first Pathway patient in December 2014. “There’s no ethical way you could go forward with this trial in people,” Cummings told Science.

StemCells, which is no longer in business, commented on a 2017 paper from Anderson and Cummings published in the journal Stem Cell Reports about the issues raised by the trial. First, said the company, the UCI animal models are not necessarily predictive of safety, and therefore should not be “the exclusive factor on which clinical testing is based.” The company noted that 10 years of data from 50 patients involving HuCNS-SC identified no safety concerns.

An embryonic stem cell line can in theory replicate itself exactly, and indefinitely. Not so with adult stem cell lines. So despite having the same name, StemCells provided batches of HuCNS-SC (derived from fetal spinal cords but considered adult cells) that did not behave the same; the clinical line used in the thoracic trial was not the same cells as the HuCNS-SC used in the Pathway Study. And neither line was the same as various research lines supplied to the UCI scientists. That’s not outside the rules of the FDA. But it raises questions about whether stem cells should be tested in vivo in animal models before clinical use. It also brings up concerns about patient safety and informed consent.

Anderson and Cummings set up the debate: suppose you are a newly injured candidate for the Pathway trial. Said Anderson, “You go to ‘Dr. Google’ to research the study, and the sponsor. You see that
Annual disease category spending, in millions, data from the National Institutes of Health

<table>
<thead>
<tr>
<th>Disease</th>
<th>2012</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>2593</td>
<td>2807</td>
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<tr>
<td>ALS</td>
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<tr>
<td>Alzheimer's</td>
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<td>Autism</td>
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<td>Parkinson's</td>
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<td>SCI</td>
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<td>79</td>
<td>99</td>
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<tr>
<td>Violence</td>
<td>154</td>
<td>111</td>
</tr>
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</table>

that if we can stimulate the right pathway, we can get the desired effects without getting unwanted side effects – we’re not flooding the system with a drug. I recently heard a talk by Dennis Choi [neuroscientist at Stony Brook and former Vice-President of Neurosciences at Merck] who pointed out that pharmaceutical companies are pulling out of neuroscience. Their drugs have not been wonderful money makers as they had hoped. They have two real big problems, he said. One is that you can’t really separate the effects you are after with an experimental drug from the side effects, especially in the brain. The other thing that happens in the neural system is that it adapts – if you give the system drugs, it eventually adjusts the receptors; it adjusts the pathway. The brain wants to go back to the way it was.

So all of a sudden, device research is springing up, and device companies are springing up, because this has the hope of solving the problems that pharmaceuticals couldn’t solve. Maybe if we stimulate the right pathway with the right frequency, we’ll only get the specific result that we want. And maybe the brain or spinal cord won’t adapt to that stimulation, it will just get better and better.

I’m a little cautious about bioengineering being the fix, because we just don’t know enough about implementation or mechanisms of action. I think it’s exciting and it’s got a lot of advantages as a new field. But we have to take some of the lessons that we’ve learned along the way with cells, biologics and pharmaceuticals, and make sure that we don’t abandon other strategies to jump on a new bandwagon just because it’s new.

— Sam Maddox
Lessons and Caution from Failed Stem Cell Trial …

from page 10

HuCNS-SC produced a positive result in the thoracic study. You assume those are the same cells you’ll be getting in the cervical trial. You are wrong.” No disclosure is made in any informed consent paperwork that explains the variability, which is also consistent with FDA policy; no such disclosures are required.

The FDA recognizes that potency testing is time-consuming and expensive for cell products because their activity can involve multiple modalities. The agency therefore does not require potency assays for early stage clinical trials. Not knowing the potency, of course, opens the door to variability.

Potency also implies that the mechanism of action (MOA) is understood, which in the case of stem cells is very unclear. Anderson and Cummings understand that scientists will never test anything if they have to know exactly how it works.

“We still don’t know what aspirin does,” Anderson said. Nonetheless, there may be a built-in disincentive for companies and researchers to try to understand MOA; this could contribute the failure of trials.

At the least, Anderson and Cummings suggest, stem cell lines should be open to more transparency, both on the manufacturing side and in pre-trial testing, with standardized reference numbers and labeling.

The Pathway Study failed to show efficacy in humans. Said Anderson, “We won’t ever know if this failure was because the neural stem cells were not effective for human spinal cord injury, or if the wrong cell line was tested prematurely in humans.”