



Progress in Research

LOOKING BACK, FOCUSING AHEAD: PROGRESS, RETURN ON INVESTMENT

By **Susan Howley**

Executive Vice President, Research

The Christopher & Dana Reeve Foundation is a business, perhaps not in the usual sense, but we do raise money from the public and we make what can be considered investments on their behalf. We are very motivated by the bottom line. In other words, we ask people to support our work developing therapies to improve the function, health and well-being of people with paralysis. The task is difficult but the payoffs are



Susan Howley

tangible. They are happening now and the momentum is building as we continue to fill our pipeline with new and potentially better therapies.

Over the course of the nearly 30 years we've been at this, the Foundation has become an investment house of scientific progress and hope. As the director of the Foundation's research strategy since the early 1990s, I can attest that we are show-

ing a robust return on investment.

Let's take a moment to follow the evolution of our research portfolio which, through its breadth, has allowed us to drive and leverage the momentum of scientific progress and move more quickly from laboratory to clinic. Through its balance, our research agenda reflects the heterogeneous nature of spinal cord trauma, a hugely complex, multifaceted problem that cannot be solved by a narrow research approach.

In the Foundation's formative years (known then as the American Paralysis Association) there was great emphasis on regeneration research; the primary goal was walking. That goal has not been foreclosed by modern science but today the notion of recovery is more nuanced; indeed, now we speak of incremental cures instead of "the cure." Promoting recovered bladder function *is* a cure; weaning a patient off a respirator *is* a cure; stopping the pain that so often accompanies injury *is* a cure.

From the outset, the Foundation has funded research that has led to a better fundamental understanding of basic biology and what is necessary to repair the spinal cord. We have invested heavily in figuring out how nerve fibers grow and connect to targets. We funded early work in the area of neuroprotection, learning how to rescue nerve cells from the body's toxic secondary response to trauma. That research continues today and is in fact the focus of the Reeve Foundation's first clinical trial. Read about our North American Clinical Trials Network (NACTN), an investment we began in 2004 to create the systems and organiza-

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FIRST NACTN CLINICAL TRIAL SET FOR SPRING

The Reeve Foundation's North American Clinical Trials Network for the Treatment of Spinal Cord Injury (NACTN) will enroll patients in its first clinical trial this Spring.

The Phase I trial, which will test the safety of the drug riluzole in acute spinal cord injury (SCI) will take place at eight hospitals in the U.S. and Canada. The trial will enroll 36 patients; the drug must be administered within the first eight hours after injury.

NACTN (pronounced nack-tin) is a network of hospitals with standardized

provide a network with the unique skills and facilities to bring therapies from the laboratory into clinical trials; it is intended for the trials to be rigorous, that they provide valid evidence of the benefits and risks of the therapy, and that they are conducted in a manner that maximizes safety to patients.

The lead investigator for NACTN is Robert G. Grossman, M.D., Chairman of the Department of Neurosurgery of The Methodist Hospital, Houston and Director of The Methodist Neurological Institute.

Grossman, who speaks softly and with

effectively in animals but they never got any further." The NACTN infrastructure provides a bridge to human trials.

Over the years Dr. Grossman has been involved in numerous clinical trials, including the one in 1990 for the steroid methylprednisolone, commonly used in acute SCI. He has also enrolled patients in numerous clinical trials for traumatic brain injury.

"If all therapies had a strong beneficial effect we wouldn't need clinical trials. There are miracle drugs but for the most part the results for new therapies are not striking,

and detecting improvements is difficult. Moreover, a treatment might work in a particular animal strain but the results are going to be much more variable in humans." Timing and dosage are critical and the only way to know is to run clinical trials.

The principal investigators at each of the NACTN clinical centers, working together, have established the experimental protocols and trained the clinical staff. NACTN also includes a Data Management Center and a Pharmacological Center, essential for the riluzole trial and future trials.

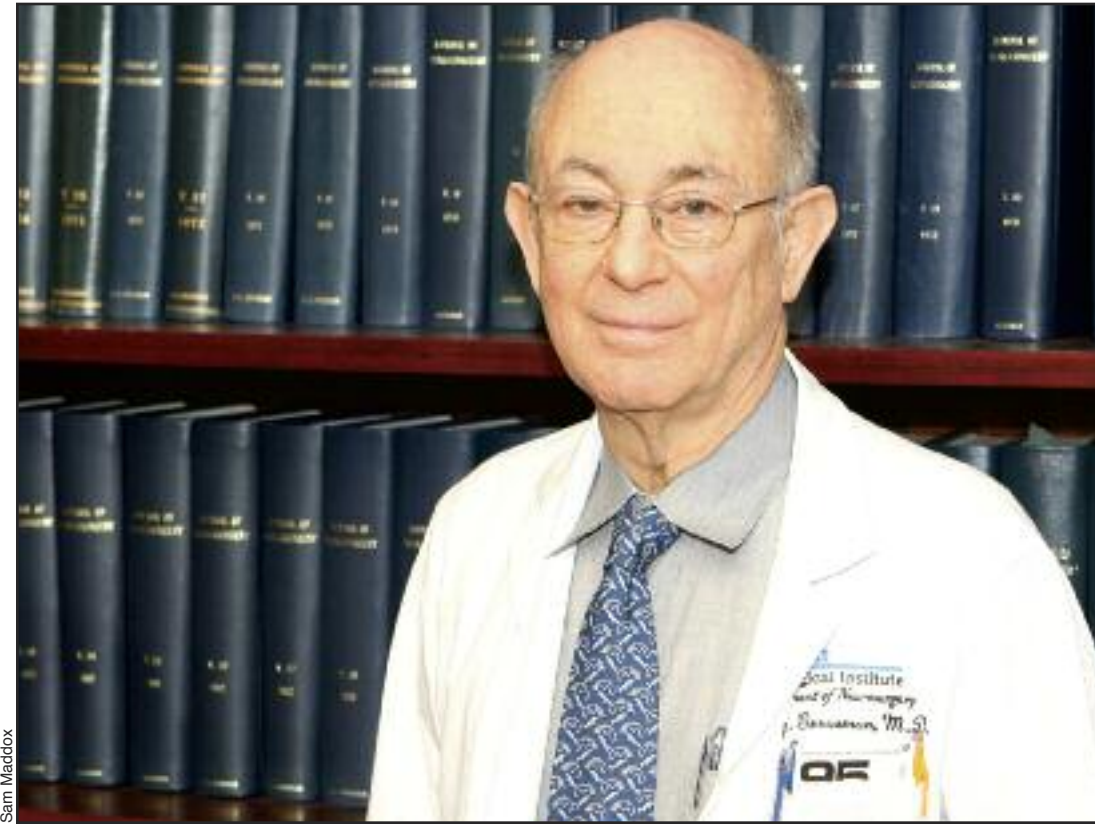
The U.S. Army Medical Research and Materiel Command of the Department of Defense (DOD) has supported NACTN since 2006. "With DOD support, the North American Clinical Trials Network has grown," says Dr. Grossman. "We have nine clinical centers includ-

ing Walter Reed Army Medical Center. DOD funding has been critical for NACTN to expand. We plan to add additional military and new civilian hospitals, and eventually VA hospitals. This will increase our capacity to conduct high-quality randomized trials with the statistical power to determine the effectiveness of emerging SCI therapies."

As of January 2009, nearly 300 patients with acute spinal cord injuries have been enrolled into the NACTN database, which contains sequential neurological examinations, the radiologi-

a hint of his native New York, has practiced medicine for over 40 years. As a young doctor, he was one of two neurosurgeons at Parkland Hospital in Dallas who examined President John F. Kennedy after he had been shot. Dr. Grossman has advised the Foundation for many years as a member of the Consortium Advisory Panel to the Foundation's International Research Consortium on Spinal Cord Injury.

Dr. Grossman saw a clear need to bring spinal cord injury treatments to clinical trials: "I saw therapies that had been used



Robert G. Grossman, M.D.

protocols and personnel skilled in the assessment and treatment of SCI. The trials network was created in 2004 by the Reeve Foundation with a consortium of neurosurgical and neurorehabilitation services of university affiliated medical center hospitals. (See list of hospitals facing page).

As a network, the basic infrastructure established for the riluzole trial will remain in place; this will in turn accelerate the process of therapy development as promising drugs become ready for trial.

The long-term goal of NACTN is to



Michael Fehlings, M.D., Ph.D.

cal characteristics of the injury to the spinal cord and to the vertebral column and detailed information about complications, with a follow-up period of a year after injury.

NACTN is structured to enable any of the principal investigators directing individual sites to be the principal investigator of a particular NACTN trial. The Principal Investigator for the riluzole trial is Michael Fehlings, M.D., Ph.D., Professor of Neurosurgery at the University of Toronto. Dr. Fehlings' laboratory studies demonstrated that riluzole protects nerve cells from the toxic cascade of events that occur in the minutes and hours after the initial trauma of SCI.

The riluzole trial design is a single arm active treatment pilot study. As is typical

in a Phase 1 study, there will not be a placebo or control group. Those in the trial will be compared to a large number of people with SCI in the NACTN database. "If the rate of adverse effects in the initial trial group is no greater than that expected in comparison with the natural history of SCI, as we know it from our database, a Phase II study of a larger number of patients will be undertaken as an efficacy trial," Dr. Grossman explains.

There are several important aspects of the riluzole trial.

- It is being supported by a state-of-the-art Internet data collection system. Each patient will be assessed on 1,200 items of information over the course of the trial. The data system is managed by Ralph Frankowski, Ph.D. and his team of biostatisticians from the University of Texas School of Public Health.

- Sensitive measurements of upper extremity function will be made with the GRASSP test (Graded Assessment of Strength, Sensibility and Prehension). This test was developed by an international team of experts in assessing neurological outcomes, led by groups at the University of Toronto and the University of Zurich. The development of the GRASSP test was supported by the Reeve Foundation.

- The pharmacokinetics and pharmacodynamics of the therapeutic agent will be measured. Says Dr. Grossman, "Previous studies of drug therapy for SCI have not measured blood and cerebrospinal fluid levels of the therapeutic drugs to determine the concentrations of



The Biostatistics and Data Management team for upcoming NACTN clinical trials, from left to right: Elizabeth G. Toups, MS, RN, Sr. Research Coordinator; Hyvan Dang, Programmer Analyst; Joy De Los Reyes, MPH, Research Assistant; Todd Weiss, MPH, Research Associate; Nina Newton, MPH, NACTN Database Administrator; Ralph Frankowski, Ph.D., Co-Principal Investigator

the drugs and to correlate these levels with beneficial and adverse effects." The pharmacological studies will be carried out by Dr. Diana Chow, Associate Professor of Pharmacology at the College of Pharmacy of the University of Houston.

Since its inception NACTN has been working with a similar SCI network in Europe, and with a network now forming in Canada. These collaborations will help form a global network that will speed therapeutic development and ensure that powerful new therapies are made available. "Clinical trials are very time-consuming and expensive and must be designed carefully to obtain valid data," Grossman says. "The key is collaboration. NACTN is a test-bed for clinicians and biomedical researchers to combine their knowledge and ultimately, to help patients."

NACTN CLINICAL SITES

The Methodist Hospital, Houston
Principal Investigator, Robert G. Grossman, M.D.

University of Texas
Memorial Hermann Hospital, Houston
Investigator, Michele Johnson, M.D.

University of Virginia
Charlottesville
Investigators, John Jane, M.D., Ph.D.
Christopher I. Shaffrey, M.D.

University of Toronto, Toronto
Investigators, Michael Fehlings, M.D., Ph.D.
Charles Tator, M.D., Ph.D.

University of Louisville, Louisville
Investigators, Christopher Shields, M.D.
Susan Harkema, Ph.D.

University of Maryland, Baltimore
Investigator, Bizhan Aarabi, M.D.

Walter Reed Army Medical Center, Washington DC
Investigator, Michael Rosner, M.D.

University of Miami, Miami
Investigator, James Guest, M.D., Ph.D.

Thomas Jefferson University, Philadelphia
Investigator, James Harrop, M.D.



Data Management Coordinating Center

University of Texas
School of Public Health, Houston
Investigator, Ralph Frankowski, Ph.D.

Pharmacological Center

University of Houston, College of Pharmacy
Investigator, Diana Chow, Ph.D.



Sam Maddox

JACQUELINE C. BRESNAHAN NAMED SAC CHAIR

Jacqueline C. Bresnahan, Ph.D., has been named chair of the Reeve Foundation Science Advisory Council. She is a senior research scientist who works alongside her husband, Michael Beattie, Ph.D., at the Brain and Spinal Injury Center (BASIC) at the University of California, San Francisco.

Dr. Bresnahan, who has served on the SAC since the early 1990s, takes over for Moses V. Chao, Ph.D., Professor of Cell Biology and Physiology and Neuroscience at New York University School of Medicine. Dr. Chao will remain on the SAC.

Drs. Bresnahan and Beattie came to the Bay Area two years ago after many years with senior academic appointments and laboratory management responsibilities at Ohio State University. “We got more and more advanced in administration – there was just more and more to do, much of it outside the lab,” says Bresnahan. “So we heard about his new opportunity and just made the decision to move west.” The transition, she says, has been exciting and exhilarating, “a bit like

jumping off a cliff while trying to figure out where to land, but it’s been intellectually stimulating at UCSF, beyond our expectations.”

The USCF neuroscience labs are directly adjacent to San Francisco General Hospital (SFGH), one of the leading trauma centers in the U.S. Says Bresnahan, “We saw this as an opportunity to use our background in the basic sciences to work alongside clinicians in state-of-the-art critical care for brain and spinal cord injury. For scientists, this is an ideal situation; it’s the place to be in order to more quickly translate our research in the

“Spinal cord injury is an extremely difficult problem, but we are trying the best we can to move things forward.”

truest sense, that is, to help patients.”

Drs. Bresnahan and Beattie are well known in the SCI research world, at least

by their last name initials. The BBB score, named for Bresnahan, Beattie and Ohio State physical therapist Michele Basso, is widely used to measure functional change in the hind limbs of animals after experimental treatments. Bresnahan and Beattie continue their work in outcome assessment, including development of new tools to assess forelimb recovery.

The Beattie/Bresnahan laboratory does basic and translational research aimed at enhancing recovery after spinal cord injury. One goal is to continue to develop preclinical models for studying treatment strategies, including transplantation of stem and progenitor cells.

Bresnahan and Beattie also focus on efforts to reduce the expansion of injury in the hours and days after trauma occurs. After the initial injury, a cascade of biochemical processes follows, including inflammation and oxidative stress. These processes continue to kill cells but they can be stopped, thus sparing vulnerable nerve tissue, and preserving function.

“Sparing is critical,” says Bresnahan. “Even saving a small amount of nervous

How individual grants are awarded

Scientists submit proposals to the Reeve Foundation. Prospective grantees must detail their experiment, the hypothesis they hope to prove, offering backup detail on methodology and justification for resource needs. They must also address the question, how does the project align with Reeve Foundation priorities. Each proposal is assigned to a couple of reviewers who give the proposal a preliminary score (one to five). The higher scoring proposals are then considered by the Science Advisory Council as a whole.

The process, normally undertaken twice a year, has been “well honed” over the years. The top projects are sent to the Reeve Foundation board for funding. “We take a great deal of time and effort to be fair and considerate,” says Bresnahan. “It is our responsibility to do the best we can with the funds raised from the community to focus study on the problems of people with SCI.”

The individual grant program allows the Reeve Foundation to leverage its resources. Says Bresnahan, “These are small grants, not a huge amount of money, but they bring young investigators into the field of spinal cord injury and allow senior investigators to change direction; as a result many new scientists are now working on SCI. Also, the grants allow investigators to take risks to go off in a new direction, get some preliminary data and then go on to get an NIH grant to continue the work.”

tissue can mean the difference between having hand function or not for a person with a cervical injury.”

Only one drug has been approved for acute SCI, a steroid whose effect is modest; the search, meantime, continues for better acute treatments (see page 2 for more on an upcoming Phase I acute trial for riluzole, supported by the Reeve Foundation).

The Bresnahan and Beattie lab is working with the SFGH trauma team to test the effectiveness of hypertonic saline in acute spinal cord injury. If it works in animals, based in large part on assessment tools developed in their lab, the treatment could move quickly into the clinic.

Bresnahan got the urge early on to pursue a career in science. She admits to being a “lab rat” who loves doing experiments and working with animals. Neither she nor her husband trained specifically to work in CNS trauma. Bresnahan began in psychology (memory and learning, how the brain produces behavior). She met Beattie in grad school as they narrowed in on physiological psychology and later, brain anatomy and motor function.

In the mid-1970s, Ohio State got a grant to study spinal cord; Bresnahan and

Beattie were drawn to the challenge. “At the time I thought the spinal cord would be easier than the brain – the input and output systems are right there.” That hasn’t really been the case. Moreover, the SCI field was not well funded, or indeed, well regarded. “At that time nobody had any hope to be able to do anything for SCI,” says Bresnahan. “The view of regeneration research was that there was not likely to be any progress in our lifetime.”

Why go on into a field dominated by such pessimism? Beattie had a cousin with a spinal cord injury, which he says motivated him. For Bresnahan, motivation came early on from people she met who were living with spinal cord injuries. “You see the consequences of something that occurs in just a moment; these injuries have such a profound effect on peoples’ lives. Spinal cord injury is an extremely difficult problem, but we are trying the best we can to move things forward.”

The business of helping the Foundation direct its scientific investments is something Bresnahan is only too happy to do.

“I think of it as my civic duty. It is an honor to serve as chair.”

WORKING ON A DREAM: KEEPING HOPE ALIVE

We need to sustain our efforts to improve the lives of those who have a spinal cord injury. Fixing the nervous system is not an easy task; this is the most complicated system in the body. Research is slowly moving things forward; people are living longer and healthier lives with SCI than in the past, and we need to keep hope that we will prevail. Breakthroughs come in unlikely places, but they won’t come if we don’t keep looking. As Bruce Springsteen says in a recent song, we are “working on a dream” and we will “make it real someday.”

Christopher Reeve said that at first your dreams seem impossible. After you work on them for a while, they seem possible, then with more work, they seem probable, and eventually they will be inevitable. We need to keep working on that inevitability and make the dream to cure spinal cord injury come true.

- Jacqueline Bresnahan



Sam Maddox

Drs. Bresnahan and Beattie



ANDREA BEHRMAN AND THE NRN: SCIENCE GIVES US HOPE

Andrea Behrman PT, Ph.D., is an Associate Professor in Physical Therapy at the University of Florida. Her specialty is adult neurorehabilitation; for nearly 30 years she has studied walking function in people with spinal cord injury. Indeed, Behrman's clinical work has helped translate the basic science that defines the Reeve Foundation NeuroRecovery Network, of which she is assistant director. In March Behrman was honored with what she calls "the Oscar" of her profession: she was named a Fellow in the American Physical Therapy Association for her lifetime achievement. In the following article Behrman discusses her work, the NRN, and hope, with Foundation staffer Sam Maddox.

Where did your interest in neurorehab and recovery originate?

Behrman: Back in the early 1980s there was a shift in the spinal cord injury population; because of better emergency management there were many more incomplete injuries. These people were walking more, moving their toes more, etc. It seemed to me that we as therapists needed to find ways to better encourage their greater potential. Textbooks did not address this potential, but focused pre-

dominantly on rehabilitation for individuals with complete injuries. My first two patients as a therapist included one with a complete SCI and one with an incomplete SCI. They still guide my thinking today.

What was a 1980s therapist doing?

Behrman: Twenty years ago in rehab, our only goal was to strengthen and build endurance for every muscle still under voluntary control. Basically, we taught strategies – compensatory strategies – new ways for eating dressing, transferring, moving around in the community, using a wheelchair, etc. The concept was that patients have to compensate for weakness. We have moved, or are starting to move, from compensation to taking advantage of own biology to recover function – that's a huge shift, and it's still going on; it will characterize rehab for the next 20 years.

What is behind activity-based therapy?

Behrman: Basic scientists wanted to understand the nervous system and how it controls movement and, in particular, walking. In animal experiments they

showed that the spinal cord makes a contribution to the control of locomotion; the cord has its own circuitry apart from the brain that can generate a stepping pattern. When a cat with a severed cord (a complete injury) is placed on a moving treadmill with its body weight supported, it can be trained to walk with repetition and practice. Now, that cat cannot jump off the treadmill and go climb a fence or chase mice; it still needs an intact connection from the brain to the spinal cord to walk at will. The activity refers to the practice of the specific task of walking and the nervous system's response in generating muscle activity (trunk control and stepping) below the level of the lesion.

So the spinal cord is not a passive set of nerve fibers...

Behrman: We used to believe the brain would issue the executive command to walk, that the spinal cord was more like a telephone cable and simply carried brain commands to the muscles. It turns out the spinal cord is not just a cable but actually is, to some degree, "smart." If the sensory information that is provided to

the spinal cord looks like walking, the spinal cord can recognize this information and respond by generating a stepping pattern of muscle activity. If you repeat this patterning, in this case with guided stepping on a treadmill, the individual can sometimes regain locomotor function. The therapy is not readily available in most clinics today; it is however the centerpiece of the NRN.

We hear dramatic stories. You published such a report last year, right?

Behrman: A young boy with a gunshot wound at the C6/7 level was referred to us. He was four and a half and had been in a wheelchair for 16 months. By every clinical measure, by every standard rehabilitation protocol, he was non-ambulatory and it was predicted that he would not walk. We started to train him on the treadmill. After 20 sessions we really had no progress; we were starting to get frustrated. Personally, I had to fight the urge coming from the standard clinical data, from the facts we had, that said this wouldn't work. That is so ingrained in us. After a few more sessions we could elicit a spinal step but it was not willful. I turned to the boy and asked, "Can you get it going on your own?" He shook his head no. But just then, he took 15 steps! Now he's ambulatory full time, though he can't walk backwards or side to side, and his balance is not good. He will be back in our clinic this summer to see how much further he can go with booster sessions of training. What we learned from this is what is possible. All tests and all standard thinking said that he would not walk. But it was possible in this child given the right training environment, experience, practice, and family support.

Someday shouldn't you know before treatment whether a person will benefit?

Behrman: What we need are better assessments – what could we have measured to know what this boy had to work with? We're still trying to learn how to tell which people will benefit from locomotor training, which will not, and what sort of training intensity is needed, within what time frame, for the best outcome. We also need a better ruler to measure the outcome itself; the current methods of evaluation are based on compensation for lost function and don't take into account recovery of function.

Walking isn't the mantra, though.

Behrman: Right. There are other health benefits that come along with locomotor training, including cardiovascular health or the ability to control your trunk better whether sitting or standing. And a successful locomotor training or outcome may mean that after training the individual walks more like he or she did prior to spinal cord injury. Generally, people also see gains in their daily, functional mobility and the amount of time they stand and walk. They may still require some assistive device because of the community they live in, for example, for uneven terrain. Not every one ambulates, of course. Will every type of injury benefit? Not everyone will walk, however, everyone is likely to show some benefit.

What is your role at the NRN?

Behrman: The NRN, funded through a cooperative agreement with the Centers for Disease Control and Prevention, is a collaboration between neuroscientists, such as Susan Harkema, clinicians, physicians, SCI program directors, and clinical scientists, such as me. The program hopes to form a road map to recovery and improved quality of life via activity-based therapies, validated by the evidence and able to be replicated anywhere. My primary responsibility is to standardize the locomotor therapy across the seven NRN clinical sites and to



advance the therapeutic program at each site. We want to make sure we provide the same therapies to acquire standard data and standard outcomes to evaluate the program's effectiveness. We teach therapists techniques and training protocols and hope thereby to foster wise, evidence-based clinical decision-making. I also chair the Pediatrics Committee within NRN that aims to provide locomotor training to children and evaluate outcomes.

What advice would you give to somebody with spinal cord injury or a stroke?

Behrman: Stay at the best level of fitness that you can. You never know what advance is coming down the road. Persons who have joint and muscle flexibility and are more fit will be in a better position to accept the opportunity to pursue whatever therapy may be available in the future.

How does science offer us hope?

Behrman: Scientific evidence helps direct us to make good decisions for patient care and rehabilitation — science directs clinical practice. By translating the basic principles of the stepping function in the spinal cord to a therapeutic intervention, it changed our mindset about the potential of the nervous system and our assumptions of what a person can and cannot do. Those assumptions give us hope – real hope for changing outcomes for people with spinal cord injuries.

HARKEMA AWARDED

Susan Harkema, Ph.D., was awarded the Reeve-Irvine Research Medal last month. The medal is awarded each year by the Reeve-Irvine Research Center at the University of California, Irvine, to individuals who have made recent and critical contributions to promote the repair of damaged spinal cords and recovery of function. The medal was also given to Canadian researcher Hugues Barbeau.

Harkema, a neurological rehabilitation researcher at Frazier Rehab Institute and the University of Louisville, directs the Reeve Foundation's NeuroRecovery Network (NRN). Her focus is on retraining people to stand and step after spinal cord injury.

Barbeau, from McGill University in Montreal, studies the physiology of the spinal cord as it relates to locomotion.

Harkema, Barbeau and NRN Assistant Director Andrea Behrman are co-authoring a book, "Locomotor Training: Principles and Practices."

REEVE CONSORTIUM'S BOLD STEM CELL INITIATIVE

In March, the Christopher and Dana Reeve Foundation joined the scientific community in hailing President Obama's lifting of the restrictions on Federally-financed research on human embryonic stem cells. Yet long before the President acted, the Foundation had laid the groundwork for devoting more resources



Samuel L. Pfaff, Ph.D.

to stem cell studies.

Whether extracted from embryos, derived from adult cells, or awakened from dormancy in the body's depths, human stem cells promise to usher in an age of regenerative medicine. Because these primitive cells can differentiate into all 200 of the known cell types, scientists may one day be able to prod them to spin off the specialized cells that will become bone, a heart valve, or any other replacement for an injured or diseased body part. Indeed, for some serious conditions caused by a single type of missing or misbehaving cell—like insulin-secreting cells in Type I diabetes—stem cell therapies already are on the horizon.

Yet huge challenges remain before these cells can be used safely and reliably in people with spinal cord injuries, which

are among the most complicated traumas that the body can endure. In theory, these cells would be part of a series of treatments designed to contain and mop up the messy disaster scene that a spinal cord injury had left behind, to recreate the intricate chains of neurons and their support cells that comprise the spinal cord, and then to restore lost function.

Recognizing both the enormous potential of stem cell therapies and the invaluable role the cells can play in research, the Reeve Foundation convened a panel of international experts on stem cell biology in 2007. Participants included prominent researchers from the public and private sectors as well as physician-scientists who treat people with spinal cord injuries.

"We asked the distinguished participants to help us clarify our priorities and to suggest the steps we should take to accomplish them," said Susan Howley, executive vice president for research at the Foundation. "The white paper that emerged from the workshop guided our Board's strategic decisions about how best to invest more resources in stem cell research."

Based on the workshop's recommendations, the Foundation launched a major stem cell initiative last year, building on the multi-disciplinary talents and cutting-edge laboratory facilities of its International Research Consortium on Spinal Cord Injury. The initiative has three components:

- Fred H. Gage, Ph.D., a veteran spinal cord researcher and a member of the Consortium who is based at the Salk Institute, in La Jolla, CA, agreed to redirect his work for the Consortium to focus more on stem cell research, particularly on experiments with human embryonic stem cells.

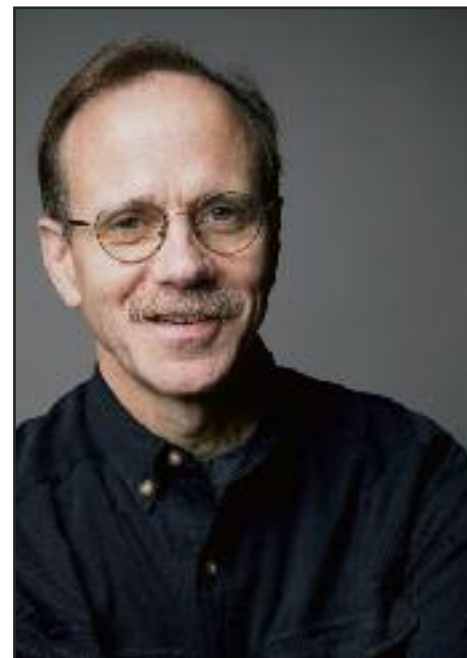
- Samuel L. Pfaff, Ph.D., an expert in stem-cell biology and neurodevelopment, became the eighth member of the Consortium. The addition of Dr. Pfaff

and his experienced staff, also at the Salk Institute, complements the work of other researchers, paving the way for collaborations involving stem cells.

- A core laboratory, dedicated to stem cell biology, was set up at the Salk Institute under Dr. Gage's direction. The new core supplies undifferentiated stem cells and stem cell expertise to Consortium scientists, and it is a training ground for the young researchers who work under them.

The Reeve Foundation initiative reflects the growing importance of human and animal embryonic stem cells in basic and applied research. In the spinal cord field, they enable scientists to study how the human cord is assembled in the first place and to identify and test potential treatments for injuries. Experts say that these investigations are likely to bear fruit before scientists learn how to use the actual cells, safely and with predictable results, at the bedside.

For example, Dr. Gage has been coaxing human embryonic stem cells in laboratory dishes to become motor neurons and their support cells and then to form working spinal circuits. In the body, these circuits transmit signals from the brain and spinal cord to the muscles involved in walking and other voluntary movements. Dr. Gage and his colleagues use these



Fred H. Gage, Ph.D.

Courtesy: Salk Institute for Biological Studies



Aileen Anderson, Ph.D.

Sam Maddox

tiny in vitro models to observe precisely what happens when the axons are cut, and then these scientists can screen various drugs to see if they limit the severity of the damage. Such experiments would be impossible with human subjects.

"We already have come up with compounds that decrease the highly damaging inflammatory response to injury," Dr. Gage explained, adding that, in a person, this response continues for weeks and amplifies the severity of the injury. "The next step is to share these findings with the researchers who use animal models to see if our potential treatments work in vivo. This is a whole new approach to science, going from human cells to animals, but it is a necessary step to test for effectiveness and safety."

Dr. Pfaff, who heads the Gene Expression Laboratory at the Salk Institute, describes his main role in the Consortium as "enhancing the tools, technologies, and experimentation" that are available with stem cells. "Our current interest is in how we might create useful cell types and how those cells might be reintroduced into the injured spinal cord," he says. "The good news is that we already know enough about the signaling and molecular mechanisms so that we can turn embryonic stem cells into motor neurons with high efficiency."

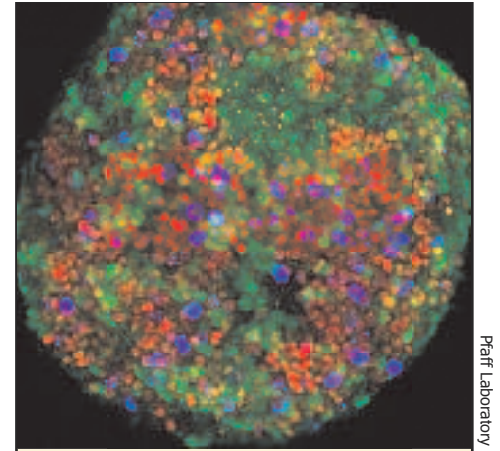
In his research, Dr. Pfaff uses mouse embryonic stem cells to study how neurons are generated, put out axons, and link up to one another. His goal is to apply the "same tricks" that occur during the embryonic stage to restore all the elements of the spinal cord. He notes that one advantage of working with mouse

cells is the availability of several lines that have been engineered to have genetic markers, which makes it possible to track the cells as they differentiate. Moreover, mouse motor neurons mature in seven to eight days, compared to 35 days for human cells. This accelerated pace also reduces the number of variables that may alter the cells. Dr. Pfaff emphasizes, however, that what he gleans from mouse cells has direct parallels in human cells. "Our end game is to get this into a therapy using human cells."

He already is collaborating with Aileen Anderson, Ph.D., who runs the Consortium's Injury Core Laboratory, located at The University of California-Irvine. Using Dr. Anderson's mouse models, they are transplanting Dr. Pfaff's stem-cell derived motor neurons into the injured spinal cord. They are testing whether the long axons that motor neurons project will stay within the spinal cord—they normally head out for muscles—and bridge the gap the injury makes. The two scientists are hopeful that spinal neurons will latch onto the transplanted cells and extend along them to rewire lost spinal circuitry. The new stem cell core laboratory is designed to support such collaborations. It cultivates stem cells in a highly controlled environment, which is particularly important for human cells because their long incubation increases the chance that something may go awry. The staff is skilled in maintaining the cells in their undifferentiated state so they can be handed off to Consortium members to generate the cell types they want to study. The laboratory also supplies the growth medium for the cells, which has to be very carefully monitored, as well as the so-called feeder cells that nourish stem cells and act as a scaffold to support them while they develop.

President Obama's Executive Order will make it easier to accomplish exchanges among laboratories, whether they are in the same building or thousands of miles apart.

"Thanks to the President's action, all our communication and collaborations will be more efficient," said Dr. Gage. "We no longer will have to maintain completely separate facilities for our work on the limited number of stem cell lines that were approved for Federal research and others that could be used only in studies funded by private sources."



Pfaff Laboratory

A cluster of spinal neurons generated from mouse embryonic stem cells in culture. The colored 'dots' represent individual nuclei of cells that have been labeled with fluorescent probes

STEM CELL PRIMER

Stem cell: a cell from the embryo, fetus, or adult that under certain conditions can reproduce itself for long periods. Can give rise to specialized cells that make up the tissues and organs of the body.

Pluripotent stem cell: can give rise to the cells that develop from the embryonic germ layers, from which all the cells of the body arise.

Induced pluripotent stem cell: a type of pluripotent stem cell derived from an adult cell such as a skin cell, by expressing certain genes that reprogram the cell. iPS cells are believed to be identical in many respects to embryonic pluripotent stem cells, including the ability to form all cells in the body and to reproduce themselves indefinitely.

Embryonic stem cell: derived from an early (4- to 5-day) embryo called the blastocyst. Cells of the inner cell mass can be cultured into embryonic stem cells.

Embryonic germ cell: derived from fetal tissue, specifically from the primordial germ cells that develop into the testes or ovaries.

Adult stem cell: an undifferentiated (unspecialized) cell that occurs in a differentiated (specialized) tissue, renews itself, and becomes specialized for the cell types of the originating tissue.

Progenitor or precursor cell: occurs in fetal or adult tissues and is partially specialized. When a progenitor/precursor cell divides, it can form similar cells or it can form two specialized cells, neither of which is capable of replicating itself.

NEW RESEARCH GRANTS

Mapping of synaptic connectivity between descending neurons and mammalian spinal interneurons using photostimulation and optical recording.

Funded for two years; \$150,000. Truly an international effort: The lead investigators are Joel Glover, an American, and Marie-Claude Perreault, a Canadian, both professors at the University of Oslo. Two graduate students funded by the grant are from Norway and Hungary.

If it is possible to regrow a nerve, is it then possible for that nerve to make the correct connection? Surprisingly little is known about whether nerve fibers (axons) regrowing from the brain make appropriate connections. This innovative basic science project hopes to describe how growing axons hook up with specific populations of lumbar spinal interneurons in mammals. Until this is understood the concept of regeneration is missing a key element.

A great deal of research effort in the past two decades has been focused on finding ways to promote regrowth of the severed axons. However, regrowth is not a complete solution, because to regain function the nerve fibers that regrow must also connect with the proper target nerve cells in the spinal cord. Therefore, information about how descending fibers normally connect to spinal interneurons (which make up most of the functional circuitry in the spinal cord) is crucial for designing strategies for promoting regeneration or compensation following spinal cord injuries.

Mapping the connections on to spinal interneurons has been very difficult be-

cause the classical techniques for identifying and characterizing the connections have been inefficient and tedious. The key to the project is the use of state-of-art photostimulation, functional imaging and electrophysiology to follow growing axons and map them as they connect with spinal nerves. The experiments will provide much new information about the way the brain connects to the spinal cord normally, and will set the stage for doing similarly rapid analyses of the correctness of connections made after nerve fibers regrow after a spinal cord injury.

Non-hormonal gender differences in SCI and sulfonylurea therapy.

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

Principle investigator: J. Marc Simard, M.D., Ph.D., University of Maryland School of Medicine, Neurosurgery.

This project proposes to run a set of animal experiments to treat acute spinal cord injury with a drug that has in previous studies limited the damage of trauma. The drug has been widely used for many years to treat diabetes. Dr. Simard, a neurosurgeon, also wants to show why males with SCI have poorer outcomes than females, unrelated to hormones.

Several years ago Dr. Simard's lab discovered a type of ion channel in the injured spinal cord (called SUR1-regulated NC_{Ca-ATP}) that is related to cell death due to cellular bleeding in the minutes and hours after trauma. His team also found a way to block the channel's action with a drug called glibenclamide (glyburide). When given soon after severe cervical injury, this resulted in a "striking reduction in hemorrhage and improvement in functional outcome," says Dr. Simard.

This proposal will test glibenclamide at various times after injury in an animal model of SCI to see if delayed treatment (at two and four hours after trauma) retains the benefit observed when treatment starts without delay. If the drug is effective, it could lead to human clinical trials.

Dr. Simard and his team also



Dr. Marc Simard and patient who recovered from paralysis

want to confirm the existence of non-hormonal gender differences in a cervical injury model while demonstrating the specific role of SUR1.

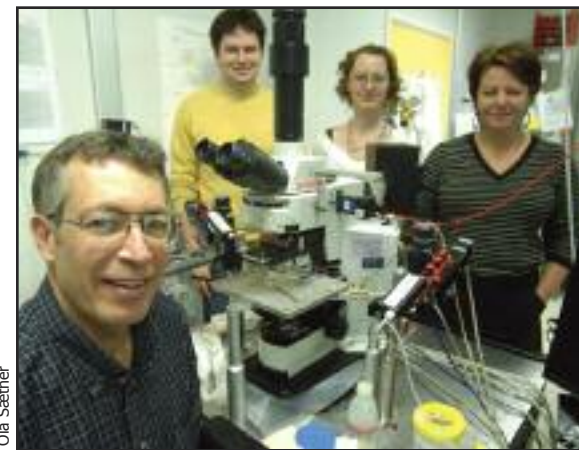
Work from other laboratories has shown that injury severity and outcome post-SCI are gender-related, with gender differences attributable in part to hormonal influences. Says Dr. Simard, new work from his laboratory has shown that in response to brain or spinal cord injury, SUR1 is found in greater amounts in males than in females.

Simard is encouraged by recent clinical experience with glibenclamide. The outcome from stroke in humans was found to be significantly improved in patients with diabetes mellitus who were taking glibenclamide and who continued on it during their hospitalization for stroke. Coincidentally, SUR1 affects production of insulin; when blocked by glibenclamide, insulin output increases, thus improving diabetes symptoms.

Dr. Simard recently treated a 17-year-old patient who came to the hospital with a rapid onset of paralysis. He had no sensation or movement. MRI showed a blood clot crushing his spinal cord. Dr. Simard gave him glibenclamide and removed the clot. Soon after the patient was able to move both legs. Less than a month later, the patient was wobbly, but walking.

"This kind of dramatic recovery was very unusual," says Dr. Simard. "I don't want to overstate the case but this shows, I believe, a benefit from our animal studies. Of course we need proper clinical trials to know. Before human trials can begin, however, it is necessary to show in animals that delayed treatment post-SCI is effective in improving outcome. The experiments proposed here are designed, in part, to address this important issue."

Tom Janski, University of Maryland



Joel Glover and team, from left in back: Ph.D. students Nedim Kasumagic and Karolina Szokol; research associate Marie-Claude Perreault

RETURN ON INVESTMENT...

from page 1

tional strategies that are essential to conducting large-scale human trials as therapies evolve (see page 2).

There was also early work funded to study cell transplantation, although the idea was more simply concerned with phenomenology (putting cells into the host and observing the effect) compared to the ambitious cellular investigations being pursued today (understanding the mechanisms by which transplanted cells, including stem cells, can promote recovery). Among other things, the Reeve Foundation's International Research Consortium on Spinal Cord Injury, a collaborative research network between leading labs around the world, addresses stem cells and their great promise (see page 8 for details on the newly launched stem cell initiative).

There was no early work funded on inhibitory factors; it wasn't until the late 1980s that Martin Schwab discovered an inhibitory molecule (Nogo) that stopped nerve axons in their tracks. Schwab also figured out how to inhibit the inhibitor, thus paving the way for a

possible treatment, now in a Phase I safety clinical trial. (Nogo was the first of several inhibitory molecules to be identified.) NACTN hopes to participate in the future Phase II anti-Nogo trial.

While we continue to explore the mysteries of basic cell biology of the nervous system, we also recognize the importance of rehabilitation in the recovery process. Research into rehabilitation once meant building better wheelchairs. The Reeve Foundation helped pioneer the idea that activity and rehab are in and of themselves therapeutic. This concept forms the basis of the NeuroRecovery Network (NRN), the Foundation's audacious and elegant effort to develop and deliver evidence-based, activity-based therapies. The NRN is having notable success changing and improving the lives of patients who participate in its Locomotor Training program. See page 6 for more on NRN co-director Andrea Behrman and this unique initiative.

For those reading this edition of Progress in Research — including our investors and shareholders — you will get a sense of where we have been. Of course

we are not about looking back. It's what's ahead that matters. We have triumphed over "dogma" (once injured, the cord could not be repaired) and we continue to build on our considerable basic science knowledge that *will* lead to effective treatments and cures. We have primed the pump for translation to the clinic. We, but most especially those living with spinal cord injury, are already seeing a return on investment.

We hope you share our excitement and we urge you to join us.



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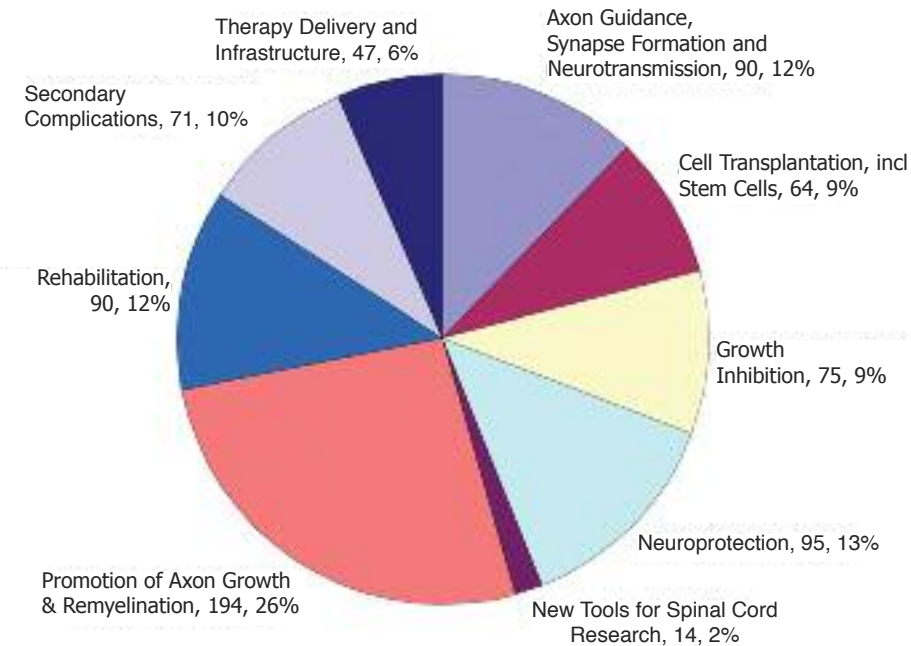
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This graph shows the breadth of the Reeve Foundation research program over the years. Each color represents an area of scientific specialization, with the number of grants made in that area along with the percentage among all grants.

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The Science Advisory Council is a distinguished panel of neuroscientists that provides expert advice to the Reeve Foundation Board of Directors with regard to funding individual research grants.

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