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 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 showing 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 organize...
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 ‘nak-tin’) is a network of hospitals with standardized 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 NACTN 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 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 effectiveness 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 Material 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 including Walter Reed Army Medical Center. DOD funding has been critical for NACTN expanded. 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 radiological 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 I 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 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.”
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."

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 UCSF 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 lab to the clinical setting."

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

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 Baso, 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 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 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."
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 clinical 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 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 theory. But, 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 and was walking 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.

Somebody 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 tell you what sort of training intensity is needed, within what time frame, for the best outcome. We also need a better way 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 mobilization and the amount of time they stand and walk. They may still require some assistance 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 may open the window of 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.
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-fi-

nanced research on human embryonic stem cells. Yet long before the President acted, the Foundation had laid the groundwork for devoting more resources
to stem cell studies. Whether extracted from embryos, de-

rived 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 replace-

ment for an injured or diseased body.

• Fred H. Gage, Ph.D., a veteran spinal cord researcher and a member of the

Institute, in La Jolla, CA, agreed to redirect his work for the Consortium to

spinal cord, and then to restore lost function. Recognizing both 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 predict-

able results, at the bedside.

For example, Dr. Gage has been coax-

ing human embryonic stem cells in labora-

tory 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

tiny in vitro models to observe precisely what happens when the axons are cut, and then these scientists can screen vari-

ous 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 com-

pounds that decrease the highly damag-

ing 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 sci-
cence, going from human cells to animals, but it is a necessary step to test for effec-
tiveness and safety.”

Dr. Pfaff, who heads the Gene Express-

sory Laboratory at the Salk Institute, de-

scribes his main role in the Consortium as “enhancing the tools, technologies, and experimen-
tation” that are available with stem cells. “Our current interest is in how we might create useful cell types and how

these cells might be reintroduced into the injured spinal cord;” he says. “The good news is that we already know enough about the signaling and molecu-

lar mechanisms so that we can turn em-

bryonic stem cells into motor neurons with high efficiency.

In his research, Dr. Pfaff uses mouse embryonic stem cells to study how neu-

rons are generated, put out axons, and link up to one another. His goal is to apply the “same tricks” that occur during the

embyronic stage to restore all the ele-

ments 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 stem cells. More recently, mouse motor neurons mature in seven to

eight days, compared to 35 days for human cells. This accelerated pace also re-
duces the time it takes to test out new treatments to alter the cells. Dr. Pfaff emphasizes, how-

ever, that what he gleaned 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 Consor-

tiun’s Injury Core Laboratory, located at The University of California-Irvine. Using Dr. Anderson’s mouse models, they are transplantsing 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 may latch onto the transplanted cells and extend along them to rewire lost spinal circuitry. The new stem cell core labora-
tory is designed to support such collabora-
tions. It cultivates stem cells in a highly controlled environment, which is particu-

larly important for human cells because their long incubation increases the

chance that something may go wrong. 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 thou-

sands 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 complete 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.”

STEM CELL PRIMER

Stem cell: a cell from the embryo, fetus, or adult that under certain condi-

ions can reproduce itself for long peri-

dods. 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 embry-

onic 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. iPSC cells are believed to be iden-

tical in many respects to embryonic pluripotent stem cells, including the abil-

ity to form all cells in the body and to re-

duce themselves indefinitely.

Embryonic stem cell: derived from an early (4- to 5-day) embryo called the blas-

tocyst. Cells of the inner cell mass can be cultured into embryonic stem cells.

Embryonic germ cell: derived from fetal tissue, specifically from the primo-

dermal germ cells that develop into the testes or ovaries.

Adult stem cell: an undifferentiated (unspecialized) cell that occurs in a dif-

ferentiated (specialized) tissue, renew-

es 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 spe-

cialized. 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.
return on investment

From page 1

Dr. Marc Simard and patient who recovered from paralysis.

Dr. Marc Simard and patient who recovered from paralysis.

NEW RESEARCH GRANTS

Mapping of synaptic connectivity between descending neurons and mammalian spinal interneurons using photostimulation and optical recording. Funded for two years; $510,000. 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 is crucial for designing strategies for promoting regeneration or compensation following spinal cord injuries.

Mapping the connections on spinal interneurons has been very difficult because 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 needed 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-homonal gender differences in SCI and sulfonfura 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 Na+ dependent action potential, or SUR1-NDAP), 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 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.

Dr. 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 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 walking, 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 experiment we are designed, in part, to address this important issue.”

return on investment

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.

Peter T. Wilderotter President

Joseph A. Canose Vice President, Quality of Life

Bill Cawley Director of Chapter Development

Stephen Coleman Vice President, Military Programs

Maggie F. Goldberg Senior Vice President, Marketing and Communications

Susan P. Howley Executive Vice President, Research

Edward T. Jober, CPA Controller

Michelle Lolantos Vice President, Human Resources and Special Initiatives

Mark Watson Vice President, Development

Progress in Research

©2009 Christopher & Dana Reeve Foundation. All Rights Reserved. 436 Morris Avenue, Short Hills, NJ 07078 Toll-free: 800-225-0292 www.christopherreeve.org

Produced by Sam Maddox/Reeve Foundation

I R Ola Sæther

formation or compensation following spinal cord injury, it must also connect with the proper target nerve cells in the spinal cord. Therefore, mapping the connections on to spinal interneurons is a crucial for designing strategies for promoting regeneration or compensation following spinal cord injuries. Mapping the connections on spinal interneurons has been very difficult because 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 needed 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 sulfonfura 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 Na+ dependent action potential, or SUR1-NDAP), 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 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.

Dr. 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 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 walking, 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 experiment we are designed, in part, to address this important issue.”
Reeve Foundation Science Advisory Council

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.

- Jacqueline C. Berman, Ph.D., Chair
  University of California, San Francisco

- Barbara J. Brosnan, Ph.D.
  Georgetown University School of Medicine
  Washington, D.C.

- Moses V. Chen, Ph.D.
  New York University Medical Center, New York

- Carl W. Coeman, Ph.D.
  Institute for Brain Aging
  University of California, Irvine

- Jean de Villèle, Ph.D.
  University of California, Los Angeles

- V. Reggie Edgerton, Ph.D.
  University of California, Los Angeles

- Michael G. Fahlings, M.D., Ph.D.
  Toronto Western Hospital Research Institute
  University of Toronto

- Alex Kolesnik, Ph.D.
  Johns Hopkins University School of Medicine
  Baltimore

- Rick Leib, Ph.D.
  University of California, San Diego

- J. Regine Perez-Polo, Ph.D.
  University of Texas Medical Branch, Galveston

- Samuel L. Pfaff, Ph.D.
  The Salk Institute, La Jolla, CA

- Muthukumar Ram, Ph.D.
  Invitrogen Corporation, Carlsbad, CA

- Jerry Silver, Ph.D.
  Case Western Reserve University, Cleveland

- William Snider, M.D.
  University of North Carolina, Chapel Hill

- Christine Steward, Ph.D.
  Reeve-Irvine Research Center
  University of California, Irvine

- Wulf A. Tetzlaff, M.D., Ph.D.
  University of British Columbia, ICORD
  Vancouver, BC, Canada

Consortium Advisory Panel

The CAP provides guidance to the Foundation’s International Consortium on Spinal Cord Injury.

- Albert J. Aguayo, M.D.
  Director, Center for Research in Neuroscience
  Montreal General Hospital, Montreal

- Robert G. Greenman, M.D.
  Chairman, Department of Neurosurgery
  The Methodist Hospital, Houston

- Gay M. McKhann, M.D.
  Professor of Neurology/Neuroscience
  Johns Hopkins University, Baltimore

- Charles H. Tator, M.D., Ph.D.
  Professor of Neurosurgery
  Toronto Western Research Institute
  Toronto Hospital, Western Division