



A P P R O A C H I N G H O P E

WHILE STEM CELL RESEARCH HAS BEEN AT THE CENTER OF POLITICAL CONTROVERSY FOR YEARS, RESEARCHERS HAVE BEEN MAKING PROGRESS TOWARD THEIR GOAL OF EVENTUALLY TREATING PEOPLE BATTLING MYRIAD DISEASES. WE TAKE A LOOK AT THEIR RESEARCH AT THE UNIVERSITY AND THE PATIENTS WHO INSPIRE THEM.

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By Nancy Ross-Flanigan

Scaered into Bob Schoeni's brain is one date that stands out from all the rest: July 29, 2008. Just back from a six-month sabbatical in Australia, Schoeni had ridden his bike to the U-M Medical Center for tests to ferret out the cause of some troubling symptoms. In recent months, his right hand had often become stubbornly stiff, and it seemed to be getting weaker.

"Playing tennis, I couldn't return the ball, couldn't get any power on it," recalls Schoeni, PhD'92, a U-M professor of public policy and economics and at the Institute for Social Research. "I thought my game was off, but it was consistently off."

So the tests: a battery of neurological assessments including an electromyogram, which measures nerve and muscle function. And by the end of the day, a diagnosis: amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. The rapidly progressing disease attacks the nerve cells that control muscles and affects the ability to move, speak, swallow, and breathe. Most patients die within five years of diagnosis.



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“My first reaction was disbelief, then a sense of intense grief and sadness,” Schoeni says. “I thought about my kids a lot.”

He and his wife, Gretchen Spreitzer, PhD’92, a U-M business professor, broke the news to family and sought second and third opinions. Meanwhile, friends pitched in to research treatments—from acupuncture and vitamins to riluzole, the single drug approved for treating ALS. The 20-page report they compiled contained plenty of options, but not much optimism.

“At best, treatment could offer a three-month life extension,” says Schoeni, now 47. “For someone who, the day before diagnosis, thought he was going to live another 50 years, three months doesn’t seem like a whole lot.”

Fva Feldman wants to offer Bob Schoeni more. It’s for patients like him that Feldman, a U-M professor of neurology, has ventured into the exhilarating, challenging, and sometimes controversial world of stem cell research. The necessity of that research became clear some seven years ago, when Feldman was the clinical and research director of the University’s Motor Neuron Disease–ALS Clinic.

“My frustration was that I could not offer to my patients any real hope of any meaningful ways of stopping the relentless progression of their disease,” she says. “Looking at the scientific landscape, the one potential treatment that showed real promise was stem cells.”

At that time, however, stem cell

research was severely restricted in Michigan. So Feldman spent three separate three-month sabbaticals at the University of California, San Diego, using animal models of Lou Gehrig’s disease to explore the potential of stem cell therapy. The results of that work were astonishing.

“I discovered that by placing stem cells in the spinal cord, I was able to halt in an animal the progression of this really horrible disease,” she says. Additional years of animal research followed, as did the passage of Proposal 2, the 2008 ballot initiative in Michigan that permitted human embryonic stem cell research to proceed in the state under clearly defined regulations.

Feldman and Emory University neurosurgeon Nicholas Boulis, a former research fellow in Feldman’s lab, received approval from the U.S. Food and Drug Administration for the first clinical trial of stem cell delivery into the spinal cords of ALS patients. That trial is under way at Emory, and while it’s still in early stages, Feldman hopes that the promising results seen in animals ultimately will be replicated in people.

For all their promise, stem cells are nothing magical—they’re simply naturally occurring cells doing what they normally do. But they have certain qualities that set them apart from other cells: not yet committed to any specific path, but full of potential, with seemingly boundless powers of self-renewal. In biological terms, stem cells are “unspecialized,” but they have the potential to transform into cells

with specific functions, such as muscle, brain, or blood cells. What’s more, they can keep dividing and renewing themselves indefinitely.

In their usual roles in the body, stem cells aid in tissue repair, replacing worn out or damaged cells with fresh, new ones. Their capacity for repair and regeneration, combined with the cells’ longevity, is the basis for all the excitement about their medical applications.

In Lou Gehrig’s disease, for instance, the effect of introducing stem cells is something like bringing vigorous new families into a decaying neighborhood.

“The large nerve cells that, in this disease, become diseased and eventually die sit in a neighborhood of other cells called ‘glial cells,’ which support the large nerve cells,” Feldman explains. “Researchers aren’t sure whether it’s the glial cells that become sick and can’t support the nerve cell or it’s the nerve cell that becomes sick and the supporting cells go awry, but somehow the whole neighborhood of cells becomes diseased.”

With the stem cell transplantation method being used in the UM-Emory study, “we introduce new, healthy neighbors into the neighborhood,” Feldman says. “It’s clear that the stem cells enter the spinal cord neighborhood and form healthy connections to the diseased large nerve cells, allowing them to stay healthier for a longer period of time. They also appear to keep the supporting cells healthier.”

Stem cell transplantation could have similarly beneficial effects in other

STEM CELLS

DIFFERENT TYPES, DIFFERENT TALENTS

Embryonic stem cells, which can divide to produce more stem cells or transform into any type of body cell, are found in the five- to six-day old embryo, called the blastocyst. Their versatility gives these cells the greatest potential for use in regenerating or repairing tissues and organs in people. The embryonic stem cells used in research come from blastocysts left over from assisted reproductive techniques, such as in-vitro fertilization. Unless these surplus blastocysts are donated to another couple or used for research, they are discarded.

Adult stem cells come from various parts of the body, with properties that depend on their source. For example, blood-forming stem cells come from the bone marrow, where their regular job is generating infection-fighting blood cells and providing new recruits for the billions of blood cells that must be replaced daily. Because adult stem cells are more specialized than embryonic stem cells, their ability to give rise to a range of cell and tissue types is more limited. (However, recent research suggests they're somewhat more flexible than previously thought.) They're also scarcer and trickier to isolate and grow in the lab.

Induced pluripotent stem cells (iPSCs) are adult stem cells that have been genetically reprogrammed to behave like embryonic stem cells. The relatively recent development of iPSCs raises the prospect of reprogramming a patient's own cells and using them to repair damaged tissues, thus avoiding rejection by the immune system.

Visit www.umich.edu/stemcell/tutorial for an interactive tutorial (courtesy of the University of Michigan) that illustrates the basics of stem cells.

intractable conditions, Feldman says.

"The same technique may be applicable to Huntington's disease, Parkinson's disease, Alzheimer's disease, and spinal cord injuries, whether acute or chronic," she says. "With this, our entire approach to neurodegenerative diseases is changing."

Talk to any of the other scientists doing stem cell research at U-M, and you'll hear equally optimistic projections in a wide range of fields. In the Medical School, the College of Engineering, the School of Dentistry, and the Life Sciences Institute, researchers are buzzing about possible ways of mending diseased hearts, repairing stroke damage, and preserving or treating infertility with these versatile cells. They're also using stem cells to better understand cancer and explore new avenues to treatment.

In Paul Krebsbach's lab, the goal is growing bone. As a dentist with an interest in craniofacial defects, Krebsbach sees patients with a variety of debilitating deformities: cancer patients who've had parts of their jawbones removed, children born with a cleft palate, people who've suffered disfiguring injuries from accidents or gun shots. Currently, the only way to correct these problems is with bone grafts from another part of the body. But Krebsbach, chair of the Department of Biologic and Materials Sciences and Division of Prosthodontics in the School of Dentistry and professor of biomedical engineering, dreams of someday repairing such defects with new bone grown from patients' own cells.

His research illustrates how each of the different types of stem cells under study at U-M and in labs around the world—embryonic stem cells, adult stem cells, and induced pluripotent stem cells or iPSCs (see the sidebar at left)—has a unique contribution to make. He started out trying to persuade adult stem cells from bone marrow to turn into bone cells and heal bony defects. Along the way, he became interested in embryonic stem cells and figured out how to urge them in the same direction.

"Embryonic stem cells have the capacity to make nerve and muscle and various other types of cells, but we learned how to steer them specifically into making bone-forming cells," Krebsbach says. "We knew they had the potential to do that, but we weren't sure we'd be able to direct them. When we did, we went on to show that we could do this not just in a dish, but also in a live animal. We could implant these cells into a skeletal defect and ultimately make bone to repair the defect."

In his current work, Krebsbach is capitalizing on an advance made by collaborators Sue O'Shea, professor of cell and developmental biology and director of the A. Alfred Taubman Medical Research Institute Consortium for Stem Cell Therapies, consortium co-director Gary Smith, and chemical engineering associate professor Joerg Lahann.

Until recently, human embryonic stem cells had to be grown on a "feeder layer" of cells from another source, usually mouse cells. This was fine for basic stem cell research, but it could present problems in human studies because the mouse cells secrete poorly understood factors that may interfere with the stem cells' normal functions. Additionally, they are genetically and immunologically incompatible with human cells. The U-M researchers developed a synthetic Petri dish coating that does away with the need for mouse cells, supporting the growth of embryonic stem cells without affecting their normal activity.

Now Krebsbach is collaborating with Lahann to grow iPSCs—adult stem cells that have been genetically reprogrammed to behave like embryonic stem cells—on the synthetic coating, bringing Krebsbach a step closer to his goal of using a patient's own reprogrammed cells to repair a defect.

"There are still a lot of fundamental biological unknowns that need to be addressed before such patient-matched cells could be used," Krebsbach admits, "but they don't seem insurmountable."

CORBIS IMAGES



Genevieve Crane, MD'06, PhD'06, was still a child when it became clear that something was wrong with her father. Tom Crane, a nuclear physicist, was passionate about bicycle racing and eager to move into the over-35 class, where he'd have an advantage as a relative youngster. The whole family enjoyed hiking the trails of Bandelier National Monument, near their home in Los Alamos, New Mexico.

Then Tom started getting shaky on his bike. His coordination was off. The eventual diagnosis was multiple sclerosis, a disease that affects the brain and spinal cord. Although some people with MS have symptom-free periods between episodes, the disease showed Tom no mercy, progressively robbing him of the ability to walk, drive, work, hold up his head, eat, and interact with his family.

Motivated by her father's illness, as well as by the scientific curiosity she'd inherited from him, Genevieve trained for a career in medical research and ended up working in the U-M lab of Sean Morrison, director of the U-M Center for Stem Cell Biology at the Life Sciences Institute until recently. Research in Morrison's lab focused on understanding how stem cell renewal is regulated in both the nervous system and the blood-forming system and uncovering similarities in those regulatory mechanisms.

"We've identified a lot of the mechanisms that stem cells use to self-renew throughout life and found that those mechanisms change during aging. Those changes are partly

LEFT: TOM CRANE (STANDING AT LEFT IN BACK) WAS A PASSIONATE BIKER BEFORE HE STARTED TO FEEL THE EFFECTS OF MULTIPLE SCLEROSIS.

RIGHT: WITHIN A FEW YEARS, THE DISEASE HAD ROBBED TOM OF HIS ABILITY TO RIDE A BIKE OR ENGAGE IN MANY OTHER PHYSICAL ACTIVITIES.

responsible for the decline in the regenerative capacity of your tissues as you get older," says Morrison. "We've also refined our understanding of how cancer cells can hijack these stem cell mechanisms to proliferate out of control."

Crane's research couldn't help her father, who died just before her graduation from U-M. However, she takes comfort in knowing that she contributed to the growing body of knowledge about stem cells that may someday benefit other patients. She and Morrison also stepped out of the lab to make a different sort of contribution: an educational video about the importance of stem cell research (www.youtube.com/watch?v=5pvsQEbPuMc).

In the video, Crane family photos flashing on the screen document Tom's decline, as Genevieve laments the lack of effective treatments for MS and other neurodegenerative diseases. But she ends on a hopeful note.

"It's hard not to be excited about stem cell therapies," she says, "when you see the number of diseases that could potentially be affected by this that really don't have optimal treatments now." Feldman shares that sentiment, knowing that she finally has something to offer her patients: if not a cure today, then at least the hope of one on the horizon.

Bob Schoeni shares that sentiment. He is doing well—for now; his disease has not progressed as quickly as he'd feared. Still, he's realistic about its inevitable course and the measured pace of science, even when researchers are working as hard as they can to move potential treatments forward.

"If I progress as most people do, it isn't going to help me," he acknowledges, "so I'm less excited for me than for other people down the road. But I do believe that if there's a science out there right now where the treatment might lead to a fundamental change in the progression of the disease, it's through stem cells. And that helps me to be a little more hopeful." 🇺🇸

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