NOT QUITE CATCHING UP WITH
ROBERT FRIEDLANDER
BY DAVID R. ELTZ

EVERY MOVEMENT COUNTS

Robert Friedlander is, among other things, a neurosurgeon. Whenever he is working inside someone's brain, excising a brain tumor or fixing an artery, he is in a state of heightened awareness. In his line of work, wandering just a millimeter off could mean nicking a nerve, clipping a blood vessel, altering lives. "Every movement counts," says Friedlander, who is chair of the University of Pittsburgh's Department of Neurological Surgery.

That philosophy seems to apply to all aspects of his life. Friedlander has made every movement count in a career in which he has not only helped patients with his surgical talents, but also made important discoveries about programmed cell death and how interrupting that cascade of death may one day translate into treatments for patients with neurological diseases.

Growing up in Caracas, Venezuela, Friedlander knew early that he wanted to be a doctor and a scientist. In high school, he read an influential *Scientific American* paper on oncogenes, which convert normal cells into cancer cells, by MIT's Robert A. Weinberg. Yet, higher education

Robert Friedlander is thought to be the first neurosurgeon to do research on cell-death pathways.

PHOTOGRAPH | JIM JUDKIS

wasn't a tradition in his immediate family. His Jewish grandfather had escaped from Pinsk, Russia, after half his family was murdered in pogroms. At 15, his grandfather fled with the equivalent of $30 in his pocket and made his way to Cuba, eventually ending up in Venezuela with a wife from Brooklyn via an arranged marriage that would produce Friedlander's mother. Friedlander's paternal grandparents had escaped the Nazis prior to World War II to what would become Israel. His father eventually visited Venezuela, where he met Friedlander's mother at a high school dance and stayed to marry her.

Friedlander's parents encouraged their son to pursue his dreams. Two of Friedlander's uncles had left Venezuela to become doctors in Boston. When he was just out of high school, Friedlander applied to Brandeis University near Boston, figuring an American education would give him the best opportunities. "That's where things happen," he says.

He was wait-listed.

Friedlander had learned to speak English from his grandmother. But realizing he needed to improve his writing and reading skills in the language to get into Brandeis, he took a six-month English course in Boston. Once finished, he was accepted into Brandeis and enrolled in an ambitious dual bachelor's and master's program in biochemistry. Friedlander soon discovered he needed to improve in other areas. His first test was in calculus; he got a C+.

"I said, *Hmmm … that's not going to get me into medical school.* It was a wake-up call," says Friedlander, who buckled down, pushing himself like never before.

Between 1985 and 1987, Friedlander worked in the lab of Michael Newman, a PhD and an assistant professor of biochemistry. In Newman's lab, Friedlander learned to grow cells in tissue culture to try to understand how a normal cell became a cancer cell.

"He was always coming back to me and making suggestions and going above and beyond what the typical undergraduate would do in pursuing research," says Newman, now executive vice president of research and development at Vaxiion Therapeutics in San Diego.

Friedlander finished both his bachelor's and master's degrees in three-and-a-half years—while working with Newman and attending classes every summer in Boston—and was accepted into Harvard Medical School. At Harvard, Friedlander wanted to continue to do research. Initially, having read Weinberg's paper on oncogenes years earlier, he was interested in studying cancer. (Cancer had run in Friedlander's family.) But he also recognized that the fields of genomics and cell biology were taking off.

When Friedlander started rotations during his third year of medical school, he considered a surgical subspecialty, but the grueling hours and years of training required made him hesitate. One of his mentors, Charles McCabe, then the director of the surgical clerkship at Harvard, told Friedlander a parable about what could happen if he chose an easier path in medicine.

McCabe said: *You could choose something else and have a good lifestyle, but if you don't like what you're doing in your practice, you're going to hate waking up. You're going to hate going to work. You're going to come home maybe at 5 o'clock and be in a bad mood. And you're not going to be nice to your wife and your kids.*

Or, McCabe told Friedlander, he could pursue training that might take two or three years longer. He would have the rest of his life to become the kind of physician and researcher he wanted to be. And he'd be doing what he loved.

Friedlander took his mentor's advice. He graduated from med school in 1991 and started a seven-year residency in neurosurgery at Massachusetts General Hospital. He worked through his residency, contemplating whether to become either a neurovascular or brain tumor surgeon. Then, something else caught his attention. During a neurosurgeon update course, Friedlander attended a talk by MIT professor H. Robert Horvitz, the founder of the emerging field of cell death.

He had planned to become a stroke researcher, but all of a sudden he was a famous ALS researcher.

"It was one of those lectures ... where your heart starts beating really fast, and you're really excited about something. Something that all of a sudden opens your eyes," Friedlander says.

Friedlander was hooked by Horvitz's science. After the talk, he approached him to ask how he could research cell death. Horvitz put him in touch with Junying Yuan, an assistant professor at Harvard who at the time had a research lab in Massachusetts General. Yuan had discovered the caspase 1 pathway (a dying cell's executioner)—the first insight into the molecular mechanism that regulates apoptosis (programmed cell death), which is crucial to many biological processes, including embryogenesis. (Horvitz, who earned a share of the Nobel Prize in Physiology or Medicine in 2002, has credited Yuan with doing a third of the work that earned him the award.)

Yuan took Friedlander into her lab in 1994. Their first goal was to understand the basic mechanisms of cell death.

"When Robert first came on board, he was just a fellow who had never done any research [like this] before," says Yuan, now a professor of cell biology at Harvard. "I was really worried about him because most people in my lab were much more advanced in terms of science."

But Friedlander caught on fast. At the time, scant evidence implicated activation of the caspase cell-death pathway in neurological diseases. Figuring he was eventually going to become a stroke researcher, Friedlander, with Yuan, created a transgenic mouse model (it made a protein that blocked cell death in the brain and spinal cord); then he made the mouse have a stroke. When he did, he saw that caspase was indeed activated in neurological disease. He also discovered that if he blocked the pathway with a drug, he could protect the mouse from suffering massive cell death during a stroke and shield the mouse from neurological damage.

Working from that model, Friedlander began to think about inhibiting cell death in amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease. Other researchers had created a mouse to study ALS using the mutant SOD1 gene, which had been identified as a cause of ALS. If the gene overexpresses its protein, the mouse's motor neurons would die, and the mouse would end up with progressive neurodegeneration, then die. This disease course is similar to what happens in humans with familial ALS. Friedlander took his cell-death-resistant mouse and crossed it with the ALS mouse. The offspring lived longer. This was the first time a scientist had been able to extend the life of an ALS mouse. The results were published in *Nature* on July 3, 1997.

But the research part of his residency was ending. Yuan was moving her lab to Harvard, and he'd have to return to the hospital staff. Yet Friedlander wasn't about to give up on his studies. So he secured a small grant from the Muscular Dystrophy Association and his own small lab to

continue the studies while going back to a rigorous house staff schedule. Friedlander was able to show that blocking the gene coding for a protein called ICE in the caspase 1 pathway in an ALS mouse slowed progression of the disease, and the mouse lived longer after getting the disease.

Here was another crossroads. He was trying to finish his residency and to become a stroke researcher, but all of a sudden he was a famous ALS researcher. "That was not the plan," he says. "But if you see an opportunity, you take it."

Around the same time, other researchers had created a transgenic mouse to study cell death in Huntington's disease, which affects muscle coordination and leads to cognitive decline, psychiatric problems, and eventual death. Nancy Wexler, president of the Hereditary Disease Foundation, had seen Friedlander's *Nature* paper on ALS. She had a representative from the foundation give him a call, asking, "Would you like to do research on Huntington's?"

Years earlier, Wexler had started research near Lake Maracaibo, a brackish body of water in the eastern part of Venezuela, home to the world's largest concentration of people with Huntington's disease. Wexler eventually discovered the gene that causes Huntington's disease, and her work led to the creation of a genetic test for the disease.

The foundation gave Friedlander his first big grant. Meanwhile, the chair of Harvard's Department of Neurosurgery offered him a tiny lab, "with the ceiling falling off," and Friedlander started research on Huntington's disease. By then, he was the chief resident at Massachusetts General Hospital.

His Huntington's research produced results similar to those he'd found in ALS: The caspase 1 cell-death pathway was activated in Huntington's disease. Blocking the pathway when breeding the Huntington's mouse with the model Friedlander had created (that inhibited cell death in the brain) made the offspring live longer. So did delivering a caspase inhibitor drug to the brain. The results were published in *Nature*. Here again, Friedlander got a diseased mouse model to live longer when no one else could.

After completing his residency in 1998 and taking a position at Brigham and Women's, Friedlander went on to use mice to make the first findings that the caspase family of cell-death pathways was activated in many neurological diseases, as well as in head trauma and spinal cord injury.

Around the same time, other researchers had used minocycline—an antibiotic used for decades to treat acne and rheumatoid arthritis—to evaluate stroke. Friedlander wanted to see how the drug worked in his mice. He tried it in mice with traumatic brain injury, then his ALS mice, and finally his Huntington's mice. In each case, the animals were protected from damage and lived longer.

AMERICO TORRES/AFP/GETTY IMAGES

Venezuela's Lake Maracaibo area is home to the world's largest concentration of people with Huntington's disease.

He would eventually show that caspases don't just abruptly kill off a damaged cell. Their activity in one cell is essentially contagious, prompting the secretion of toxic substances that make neighboring neurons too sick to work properly.

Despite his success at the bench, Friedlander hasn't yet been able to demonstrate the same results in clinical trials. He has worked with others to develop drugs to block the caspase family of cell-death pathways, yet none of the drugs has worked in humans.

Friedlander says part of the problem is in the challenge of translating research from mice into humans. Although disease in mice mimics disease in humans, transgenic mice are essentially identical; they have the same disease, the same mutation. Humans, however, are not all the same. Mutations and injuries in humans vary from person to person.

Friedlander, who became chair of the neurological surgery department at Pitt in June 2010, has since been looking for other drugs that might work better than minocycline. He is collaborating with Robert Ferrante, professor of neurological surgery, whom Friedlander recruited to Pitt last year from Boston University.

In recent years, both Friedlander and Ferrante have started to think about changing the way clinical research is done. They believe researchers should stop trying to see whether just one therapy can help patients and consider drug cocktails instead. "Much of the target-centric approach that science has taken over the past 50 years really hasn't worked, because we're only homing in on one particular aspect of a disease," says Ferrante. "The current approach is to look at polytherapies. … We're finally taking that approach to patients with chronic neurodegenerative disorders."

Friedlander is currently the only neurosurgeon on the advisory council of the National Institute of Neurological Disorders and Stroke. He's also a recipient of the Society of Neurological Surgeons' H. Richard Winn MD Prize, one of many honors recognizing his contribution to science and medicine. Her Royal Highness Crown Princess Katherine of Serbia, who is known for her humanitarian projects, says, "there's not enough recognition in the world" for Friedlander.

Friedlander and his wife, Eugenia, met the princess about 11 years ago. Since then, Princess Katherine, who helps people in her country get medical care, often calls on him to assist with patient cases: "I think he was born to save lives," she says. "Every day of our lives we are grateful to God that we have gone through this life and not missed meeting him."

Friedlander, so aware of making the most of his time, says Pitt has everything he was looking for in a chair opportunity: visionary institutional support from the medical school and medical center, a vibrant neuroscience community, an institute dedicated to academic drug development, and the largest and busiest neurosurgery department in the country. Pitt is also the home of many innovations, including transnasal (entering through the nose rather than opening the skull) endoscopic skull-based procedures, the Gamma Knife, microvascular decompression, and—among the latest—high-definition fiber tracking, which is an enhanced MRI technique that for the first time allows doctors to see connectivity of brain areas in 3-D (see cover story). And his department has been recognized for its unusual productivity in basic science.

"The opportunity here is once in a lifetime," says Friedlander. ■