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Restoring Neurological Function Using Stem Cells

For decades, scientists believed the adult brain was immutable – fixed and incapable of change, especially in the face of injury. But in recent years it's been shown that the brain is a remarkably resilient organ, capable of re-designing itself to learn new skills and recover lost functions. Stanford neurosurgeon Gary Steinberg, MD, PhD, is capitalizing on that potential with an innovative approach aimed at helping stroke patients move once-paralyzed limbs, regain their ability to speak and resume daily activities. His approach relies on the newly discovered power of stem cells to spark regeneration of neurons and networks in the brain that control our ability to perform day-to-day tasks.

As a neurosurgeon, Steinberg has long been frustrated by the lack of treatments for stroke, which affect some 800,000 people a year in the United States alone. It is the fourth leading cause of death in the nation and the single biggest cause of disability. The U.S. spends roughly $100 billion a year on stroke-related costs.

The most common type of stroke, known as ischemic stroke, occurs when blood flow to the brain is disrupted, often as a result of a clot. Current treatments involve use of the drug tPA (tissue plasminogen activator) which can dissolve the clot when given shortly after the stroke or an emergency procedure in which clinicians feed a catheter through an artery and into the brain to break up a clot. After the initial therapy, patients may experience some improvement through physical therapy and rehabilitation, but most reach a plateau around six months. The conventional wisdom has been that it's not possible to regain function beyond that. As a result, there are nearly seven million people in the United States living with long-term disabilities caused by stroke.

However, Steinberg has challenged that thinking, and his latest research shows that patients may benefit from treatment well beyond the six-month window. In both animal and human studies, he has found it's possible to revive damaged brain circuits and restore lost capabilities, possibly after years of paralysis.

"After six months, we thought those circuits were dead," said Steinberg, the Bernard and Ronni Lacroute-William Randolph Hearst Professor of Neurosurgery and the Neurosciences. "Now we know they are not. That's why we think that transplanting stem cells late – years out – can resurrect function."

Pioneering Work

Steinberg is the longtime chair of the Department of Neurosurgery, as well as Founder and Co-Director of the Stanford Stroke Center. He is a leader in the development of minimally invasive and advanced surgical techniques for treating a variety of cerebrovascular conditions.

Steinberg was among the first scientists to test the value of stem cells in stroke, beginning in 2000, when there was much skepticism. Stem cells have enormous potential to regenerate lost or damaged tissues, as they can be coaxed into becoming any type of cell in the body, including neurons. Steinberg's early work in stem cells was inspired by his colleagues at Stanford, which has long been in the forefront of stem cell research. One of his early collaborators was Irving Weissman, MD, director of Stanford's Institute for Stem Cells and Regenerative Medicine and a stem cell pioneer.

In 2004, Steinberg's group published a study in which they injected human fetal neural stem cells into stroke-impaired rats and found that the cells don't do well when transplanted close to the stroke site because the environment is inhospitable. But if the cells are transplanted just a few millimeters away, they survive and are drawn to the area of the injury. The stem cells then begin to interact with immune and other cells around the stroke site, and this initiates a process that may help the animals recover, the researchers found.

The experiment was the first of many that helped Steinberg and his colleagues begin to understand the underlying mechanisms that enable stem cells to aid in repairing the brain. Early on, the belief was that the stem cells would turn into neurons and thus reconstitute lost cells and circuits. But intensive research in the lab has shown that the stem cells actually work by pumping out various types of proteins and other molecules, including very powerful growth factors, that enhance the brain's natural ability to repair itself.

These factors can help neurons grow new axons and dendrites - the nerve fibers that enable the neurons to communicate and form new pathways. They also can induce the formation of new blood vessels in areas damaged by stroke. And they can help blunt the harmful inflammation induced by stroke that can persist over many years. In effect, the stem cells help the brain revert to a younger, more resilient state, Steinberg said.

"Essentially what we think they are doing is turning the adult brain into an infant brain," he said. "Infants recover very well after strokes or other injuries. If an infant has a stroke and is paralyzed, often he or she makes a complete recovery."

Stunning Initial Results

Based on work in the lab, Steinberg has collaborated on seven clinical trials using a variety of stem cells to treat stroke, as well as traumatic brain injury and spinal cord injuries. In a stunning trial, he collaborated with investigators at the University of Pittsburgh in injecting millions of modified human adult stem cells into the brains of 18 chronic stroke patients. These patients had been debilitated by stroke for up to five years before they joined the study. The investigators used stem cells derived from human bone marrow and specially engineered for use in the trial.

The goal was to see whether these cells could be safely used in humans. Since it was designed strictly as a safety trial, the researchers were surprised to see some patients show astonishing benefits. Before the study, one 71-year-old participant could barely lift her leg and could move only her thumb on one hand. Shortly after the transplant, she was able to lift her leg high and touch her hand to her nose. Six months later, she was walking again.

A second patient, Sonia Coontz, had experienced a stroke in 2011 that left her barely able to speak, unable to raise her right arm or walk more than five minutes before needing a wheelchair. After she received a stem cell transplant, her life changed dramatically.

"It's been 4 ½ years, and I'm able to climb the stairs and have conversations with family and friends. I run. I work out. My life is amazing. I was also able to become a mother," she said in a 2017 ceremony in which she presented Steinberg with the Smithsonian's American Ingenuity Award.

Overall, 72 percent of the patients in the study had a clinically meaningful recovery, signifying they were able to participate in activities that had not been possible before the transplant, the researchers reported in a journal publication in 2016. Steinberg and his team are now looking at what factors are at play in influencing a patient's recovery. The stem cells themselves disappear within two months. But they have a lasting impact; patients have had sustained recoveries for years, demonstrating that once-dormant brain circuits can be revived.

"The key thing we learned from the study is that the circuits aren't irreversibly damaged," he said.

Steinberg and his colleagues did make a potentially significant observation when they viewed the magnetic resonance imaging scans of the brains of the study participants after transplant. Fourteen out of the 18 participants

showed a temporary bright spot in the motor area of the brain, which controls movement. The size of the spot, a kind of imaging signal, was directly related to how well the patients fared in the two years following the procedure. Steinberg said he believes it could be an area of beneficial inflammation that is spurring the formation of new neural circuits. He recently received an NIH grant to study this phenomenon and other underlying factors that may contribute to the patients' recoveries. A subsequent double-blind, randomized trial involving 163 patients at multiple medical centers, including Stanford, was just completed and investigators now are analyzing the data.

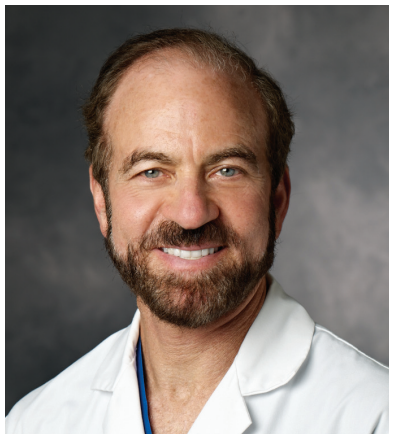
Yet another double-blind, randomized trial has been conducted using these same bone marrow stem cells to treat patients with chronic traumatic brain injuries, which affect about 200,000 Americans every year. In early 2018, investigators at Stanford and multiple other sites injected millions of cells into the brains of 61 patients with serious motor difficulties caused by brain injuries. Six months later, the transplanted patients showed significant improvement in their ability to move and perform basic activities compared with control patients, the investigators found.

A Promising New Approach

Steinberg is now on the cusp of a new clinical trial with a different kind of stem cell, derived from embryonic tissue. Steinberg developed the cell, known as NR1, in his laboratory over the last two decades and has tested it in multiple studies in animals, who recover significantly from their stroke injuries. The NR1 cells appear to have some advantages over the bone marrow-derived cells. For one, they are not genetically manipulated, thus reducing their potential to form tumors. Moreover, they can be manufactured in large quantities, Steinberg said.

Steinberg recently submitted an application to the federal Food and Drug Administration to do a clinical trial with the NR1 cells in 10 to 30 patients, all of them at Stanford. Like the previous trial, the patients will all suffer from limb weakness and movement problems related to a stroke they experienced six months to five years before the start of the study. And as with the last trial, the cells will be injected directly into the brain, which studies suggest is the most effective method of delivery (compared to injecting cells into the veins or arteries). He hopes to begin the trial in 2020.

There are many questions yet to be answered about stem cell therapy for stroke, including the best type of cells to use, the best time to deliver the cells after a stroke and the best route for delivery. There is also much to learn about the underlying mechanisms that enable the cells to be effective and the factors that influence a patient's recovery, but the results seen to date have been extremely promising.



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— Gary Steinberg, MD PhD

Future Impact

Your philanthropic investment in this groundbreaking work can greatly advance the field and more rapidly enable desperately needed treatments to reach the many patients living with stroke-related disabilities.

Steinberg also hopes that ultimately this research in stem cells may be applied in treating other disorders including traumatic brain injury and spinal cord injury, as well as neurodegenerative conditions, such as, Parkinson's disease, Lou Gehrig's disease and possibly even Alzheimer's disease. The support of generous donors like you will help bring us closer to that goal.

To discuss the role you can play in helping move this work forward, please contact Allie Gregorian, Senior Associate Director and neurosurgery fundraising specialist in the Office of Medical Center Development at Stanford University.

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