Is new therapy beginning of the end of Alzheimer's?

by Scott_LaFee

A dramatic gene therapy trial at University of California San Diego that involved injecting skin cells containing human nerve growth factor into the brains of patients with Alzheimer's disease may have taken a significant step forward.

FIGHTING ALZHEIMER'S - Adam Fleisher, an assistant professor of neuroscience who is directing new research to cure Alzheimer's disease, talks about his team's efforts. Listening are Eileen Greenwald, who received the experimental therapy, and her husband, Hugh. CNS Photo by Scott Linnett. Instead of using modified skin cells from each patient as the carrier of a gene that expresses the nerve growth factor (NGF), researchers are now employing a harmless but naturally efficient virus.

The viral approach, they say, is simpler and cheaper, and it may be more effective.

Building upon an earlier six-patient trial at Rush University Medical Center in Chicago, UCSD neuroscientists are seeking a handful of San Diego residents already diagnosed with Alzheimer's to assess the safety and efficacy of a more aggressive treatment.

One patient - a 79-year-old woman from Oceanside, Calif., - underwent treatment in November. Three more study participants are sought. They must meet at least three basic requirements:

1. They must already have been medically diagnosed with Alzheimer's disease.

2. They must be between 50 and 80 years of age.

3. They must be in general good health, without any medical implants that might hinder tests.

Alzheimer's is a devastating degenerative disease of the brain that gradually erases a person's memories and cognitive functioning. It is not considered part of the normal aging process, though its precise cause remains unknown. There is no known treatment to prevent it or cure it.

Approximately 5 million Americans suffer from Alzheimer's; more women than men. Ten percent of Americans over the age of 65 have the disease. By age 85, that figure rises to 50 percent. By 2050, some estimates project as many as 16 million Americans will be grappling with the disease.

GROWING PROBLEM

Needless to say, an effective treatment to slow the disease's progression, if not reverse it, has become something of a neurological holy grail.

In 2001, UCSD scientists made headlines by injecting genetically modified skin cells from eight Alzheimer's patients into their brains at precise sites where the researchers believed the disease was wreaking the greatest havoc.

The skin cells had been altered to express the human form of nerve growth factor, a protein found in all mammals that acts like a kind of brain-cell fertilizer. By exposing neurons damaged by Alzheimer's disease to additional growth factor, scientists hoped to prompt cells to repair themselves and grow new connections, perhaps restoring lost cognitive function.

The first trial in 2001 and 2002 was too small and limited to be conclusive, but resulting data was encouraging. Tests showed patients' brains were biologically more active, though how that played out in terms of improved mental functioning was harder to measure. Patients themselves reported improvement - or at least perceived a slower rate of memory loss - with virtually no side effects.

The new trial is also small - another safety test. But this time, there are some big differences. Patients will receive much higher doses of nerve growth factor in the form a gene therapy drug called CERE-110, developed by Ceregene Inc., a San Diego-based biotechnology company and sponsor of the study.

More critically, CERE-110 will be delivered to patients' brains via an adeno-associated virus (AAV), a virus capable of infecting humans and some primates, but not known to cause disease.

"What we've done is take just the part of the virus that acts as a transport, that lets it get into human cells. It's just a carrier of the gene for NGF," said Adam Fleisher, an assistant professor of neuroscience who is directing the new study.

"CERE-110 is injected by a neurosurgeon directly into an area of the brain known to be affected by Alzheimer's disease," Fleisher explained. "It is designed to be taken up by nerve cells in this region, which may then use the NGF gene to make NGF protein. This protein may protect nerve cells from dying, improve their function and even make them grow."

The new viral technique is likely an improvement upon the earlier skin-cell method, said Dr. Mark Tuszynski, a UCSD neurologist and neuroscientist who helped lead the 2001 study. As a founder of Ceregene, Tuszynski is not directly involved in the second trial, but he is serving as a consultant.

"The AAV vector approach is simpler because there is no need to obtain cells from each individual and expand them in culture, which requires months," he said. "Instead, the AAV vector is produced in relatively large quantities and can be used to treat any patient. This clearly reduces time and cost in implementing the

procedure."

More importantly, perhaps, Tuszynski noted that earlier monkey studies using the virus indicate nerve growth factor continued to be expressed at consistent levels for at least six years after treatment. In contrast, data from skin-cell studies indicates gene expression of nerve growth factor begins to decline gradually within the first year.

ONE WOMAN'S FIGHT

Sitting in Fleisher's office at UCSD's Alzheimer's Disease Research Center in San Diego, Eileen Greenwald listens to the talk of genes and viruses and nerve growth factor with a keen and focused expression, though frankly, it's all a bit beyond her.

In 2005, Greenwald was diagnosed with Alzheimer's.

"What we noticed first and most often was her inability to answer questions," said her husband, Hugh. "Whatever else was happening, Eileen could always ask questions. Her brain won't let her stop asking questions.

"But then she began to not remember the answers. We used to joke that she just wasn't paying attention, but the forgetfulness got progressively worse over the last 10 to 15 years."

After Greenwald's diagnosis, a family member mentioned UCSD's Alzheimer's research effort. Hugh brought Eileen for an assessment, hoping perhaps to enroll her in a trial.

"We wanted to help, but we had selfish reasons, too," he said. "We're interested in anything that might delay further onset of the disease. Our greatest hope is for recovery."

Greenwald is the first of the four patients sought for the CERE-110 trial. In November, in an eight-hour operation, doctors injected 80 microliters of AAV - 0.00541 of a tablespoon - into two sites in her brain. She went home 24 hours later, visibly no worse for the experience.

It will take much longer, however, to see if the CERE-110 gene therapy slows or reverses her disease. "It will take at least six months to a year before we'll be able to see a change," said Fleisher.

In the meantime, UCSD researchers are laying the groundwork for a second-phase trial that would be much larger and more complex, involving many more patients at multiple test sites around the country.

Greenwald smiles at the news.

Asked what she thinks about the trial, about what has happened to her and how she feels, she frowns slightly, pondering the question. Then she turns to Hugh and asks, "How do I feel?"

"Good," he replies, gently.

"Good," she answers, smiling again.

Watching, Fleisher nods and explains.

"It's not uncommon for Alzheimer's patients who are losing their memory to lose confidence in their thoughts. They stop trusting their memory. They aren't sure if what they remember is real."

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