Mice Show Alzheimer Brain Plaques

Former President Ronald Reagan and as many as 4 million others in the United States suffer from Alzheimer's disease, a progressive disorder that causes impaired thinking, memory loss, and eventual death.

The cause of Alzheimer's remains unknown. No cure exists. And researchers have repeatedly failed in their efforts to produce a suitable animal model for the disease.

Until now.

Now, Ivan Lieberburg of Athena Neurosciences in South San Francisco and his colleagues have developed mice whose brains suffer damage strikingly similar to that seen in humans with Alzheimer's disease.

"This is the holy grail of Alzheimer's research," Lieberburg says. "I never expected to see this in my lifetime."

Other researchers agree that a mouse model for Alzheimer's disease would represent a significant turning point in the scientific community's search for new treatments.

"If this new model is validated by others, it will be very useful both to explore the scientific ideas and to design and test new kinds of therapeutic agents," says Leonard Berg, a neurologist at Washington University School of Medicine in St. Louis.

Until now, researchers have had to rely on test-tube models of this disorder, says Berg, who also serves as chairman of the medical and scientific advisory board of the Chicago-based Alzheimer's Association.

Lieberburg's team began its endeavor knowing that the brains of people who have died of Alzheimer's disease are strewn with plaques. These plaques — dying nerve cells surrounding a core of protein fragments called beta-amyloid — correlate with the advance of dementia.

Lieberburg's group first created genetically engineered mice that carry the human gene coding for a precursor substance to beta-amyloid. The team then demonstrated that these transgenic mice crank out the human beta-amyloid associated with Alzheimer's disease.

Finally, the researchers looked for age-related changes in the brains of the mice. "Up to 6 months of age, we really didn't see much of anything," Lieberburg says.

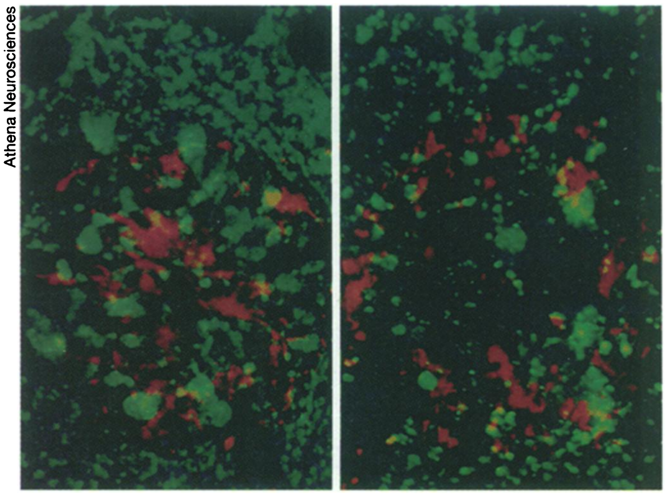
However, from 6 to 9 months of age the mice exhibited increasing deposits of beta-amyloid in certain regions of the brain, including the cortex, which is responsible for higher thought as well as memory.

Older mice had brains so littered with these amyloid plaques that they resembled the brains of people with advanced Alzheimer's disease.

Mice that had not been genetically altered showed no plaque formation.

The research team has yet to demonstrate that the genetically altered mice show any symptoms of dementia — unlike people, mice cannot forget where they've left their car keys. Still, the researchers hope to prove impairment in these animals in other ways, perhaps in their ability to find their way through a maze, Lieberburg says.

This mouse model may help scientists design a drug to block the plaque formation observed in Alzheimer's disease. Yet even with an animal model, researchers say it may take many years to find a promising drug that works in humans. — *K. Fackelmann*



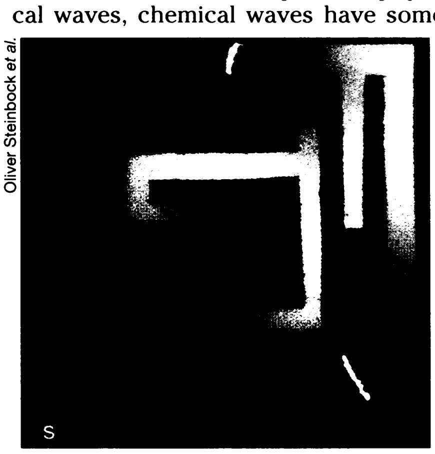
Athena Neurosciences

The mouse brain (left) shows plaque deposition, as does the brain of a person with Alzheimer's disease (right). In both photos, nerve cells are pictured in green. Red areas represent plaques with their cores of beta-amyloid, a small protein thought to kill neurons. Yellow depicts areas of overlap.

Pathfinding made easier by chemical waves

Computers can beat humans at many tasks, but they often do it by brute force. To find the quickest route through a maze, for example, a computer typically calculates every possible path and chooses the fastest. Now, researchers have found a shortcut to this computation: Just follow a chemical wave.

A chemical wave is a self-propagating reaction front that moves through certain kinds of media. Compared to physical waves, chemical waves have some odd properties: They move at a constant speed, skirt barriers without breaking up, and vanish at dead ends.



Oliver Steinbock *et al.*

Computer map of optimal distances made by combining 250 images of a chemical wave that began at S. The farthest points are blue; white lines mark equidistant paths.

A group led by chemist Kenneth Showalter of West Virginia University in Morgantown took advantage of these properties to find the shortest route through a maze. To make a chemical wave, they soaked a small square of polymer membrane in an acidic solution of bromate ions, malonic acid, and an iron catalyst. They cut pieces from the membrane, leaving the corridors of a maze.

The researchers then touched a silver wire to one edge of their maze to set off a wave and took a video image of the wave front every 10 seconds. These snapshots, fed into a computer, gave them a composite image from which they derived a grid of vectors.

"You have a whole lot of information in this grid," Showalter says. A computer might have to do thousands of trial-and-error calculations to find the shortest path in a grid that size, he explains. But using the vector field from the chemical wave, "you can pick any point at random, and you automatically know how to get back to the starting point just by following the vector flow."

"You could call it a parallel approach," Showalter adds. "You do