

# The race to save memories

RESEARCHERS SET THEIR SIGHTS ON A VACCINE AND OTHER NEW TREATMENTS FOR ALZHEIMER'S



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**U**NRAVELING THE MYSTERY OF ALZHEIMER'S DISEASE HAS been 100 years in the making. It was Nov. 3, 1906, when Alois Alzheimer, a German neuropathologist and psychiatrist, described plaques in the brain of one of his patients. Today, 4.5 million Americans suffer from Alzheimer's disease, and as life expectancy increases, that number will likely surpass 14 million by 2050.

"It's a tragedy," says Brigham and Women's Dennis Selkoe, MD, who co-directs Neurology's Center for Neurologic Diseases. "Once memory is lost, it's very hard to retrieve. So, we want to treat the disease as early as possible or, better yet, prevent it."

Selkoe has dedicated the past 25 years to understanding Alzheimer's disease, pioneering the "amyloid hypothesis"—the

most widely accepted explanation of the disease process. It states that amyloid-beta, a small, sticky protein, accumulates in the brains of Alzheimer's patients and becomes toxic to brain cells, eventually leading to the death of neurons and dementia (see illustration on page 8).

Current medications treat memory loss by regulating chemical messengers in the brain, and some patients show improvement. However, the results are usually minimal and weaken over time, and the drugs do nothing to reverse the underlying disease. Now, armed with a better understanding of how the disease begins and progresses, and with amyloid-beta as a target, Selkoe and his colleagues hope to make real inroads into managing this illness.

Researchers aim to rid the brain of amyloid-beta protein

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using two broad approaches, which Selkoe likens to adjusting water levels in a bathtub. "If a bathtub is going to overflow, you can either turn down the spigot or open the drain."

One "drain-opening" approach being developed at BWH relies on a nasal vaccine that prompts the immune system to make antibodies to amyloid-beta that will target and clear the toxic protein from the brain. In a study of the vaccine, published in the May 3, 2006, issue of *The Journal of Neuroscience*, results in mice bred to develop amyloid plaques were promising.

"We found fewer plaques in the brain, improved cognition and less neuron degeneration," says Cynthia Lemere, PhD, the study's principal investigator.

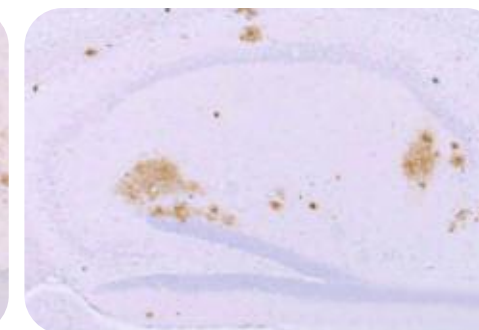
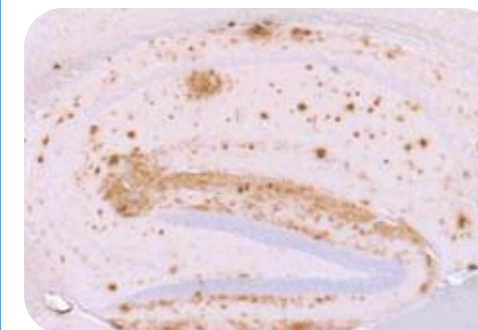
One of Lemere's primary challenges is to trigger an immune response that's safe enough for the human brain. In 2002, an

Alzheimer's vaccine trial conducted by a pharmaceutical company was called off after 6 percent of the 300 participants developed brain inflammation. Researchers believe the vaccine had triggered an immune response, but, in some people, that response was misdirected: The immune system's foot soldiers, known as T cells, had gathered en masse, causing brain inflammation.

To avoid an inflammatory response, Lemere and her colleagues designed a vaccine that uses multiple copies of small fragments of the amyloid-beta protein, which is not normally found on its own in the brain. It was just enough to coax the immune

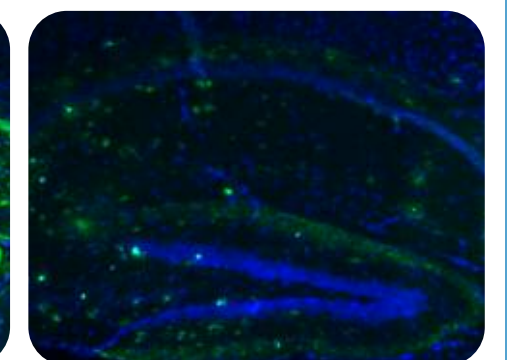
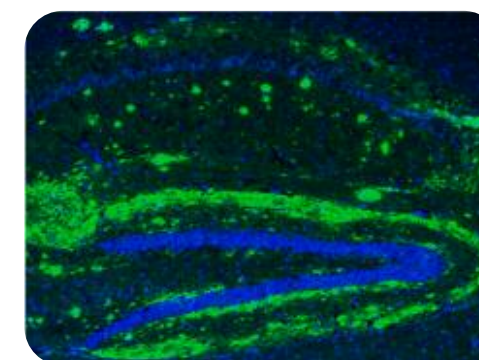
## A nasal vaccine for Alzheimer's?

Two Alzheimer's disease vaccines in development at BWH are administered using a nasal spray, which appears to prompt a more effective immune response in the brain than standard injections. Researchers agree that timing is another factor. In animal models, the vaccines work best when given early in the disease process.



At the far left, amyloid-beta clusters (in brown) are visible in the brain of a mouse with Alzheimer's disease. A mouse with the same risk for the disease received weekly nasal vaccines containing a fragment of amyloid-beta protein. This mouse, on the right, has markedly fewer plaques. Weekly treatments began at the earliest stage of plaque formation.

At right, amyloid-beta deposits, or plaques (in green), can be seen in the brain of a mouse with Alzheimer's. On the far right, a mouse treated with a nasal spray vaccine containing the adjuvant protollin has far fewer deposits in its brain. The vaccine, which was administered weekly for eight months, triggers brain cells called microglia to attack amyloid-beta.

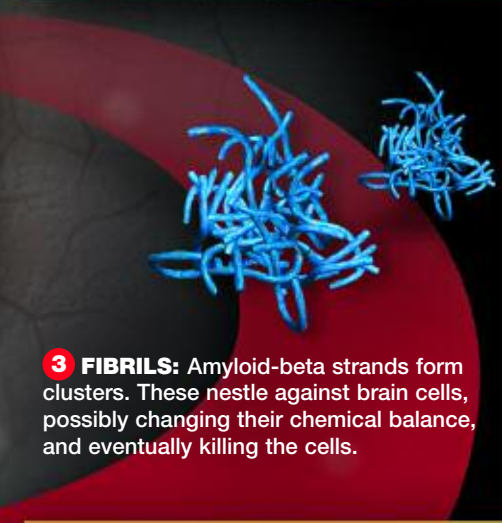
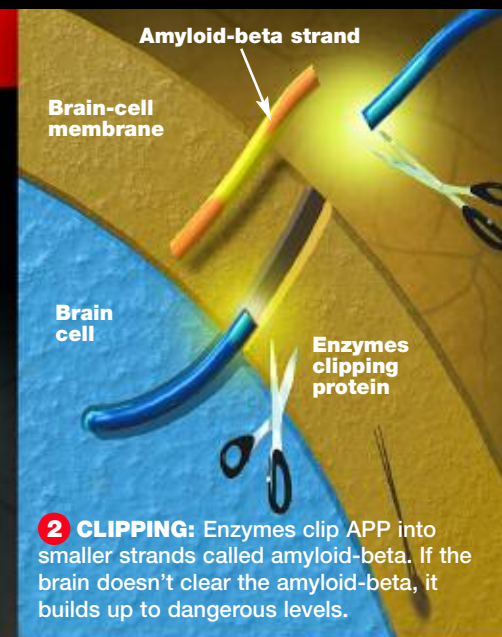
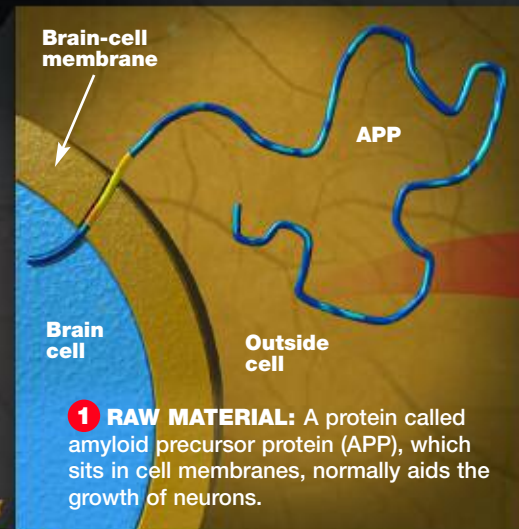


# Alzheimer's at work

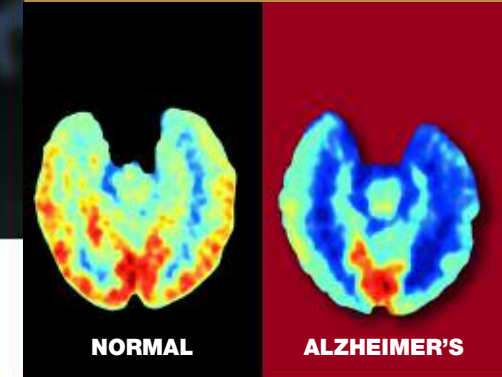
Research at Brigham and Women's is revealing some of the mechanisms behind Alzheimer's disease. Drugs to counter its effects on the brain are in development.

## Cellular changes

Alzheimer's is marked by dramatic shifts in molecular function that eventually destroy cells. New evidence shows that small clusters of a sticky protein called amyloid-beta are toxic to neurons and may be the true culprits in the disease process.



**Brain scans**  
What's the impact of Alzheimer's on the brain? Magnetic resonance imaging shows less activity (blue) in areas responsible for memory and cognition in patients with the disease than in normal, healthy adults.



**5 AREAS AFFECTED:** Cells in regions governing thought, reasoning and memory are particularly hard hit.



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DENNIS SELKOE, MD

system's B cells into making antibodies without prompting an overblown T cell response.

"Essentially, we're trying to trick the immune system," says Lemere. "The T cells only recognize the shorter fragment, and in the study, we did not see any sort of T cell response against the full-length amyloid-beta protein found in the brain."

Another nasal vaccine in development bypasses the creation of antibodies altogether. Instead, it directly activates one of the key components of the brain's own immune system—microglial cells.

"If you activate microglia, they'll eat up the amyloid," explains Howard Weiner, MD, who co-directs the Center for Neurologic Diseases with Selkoe. "It doesn't involve using the amyloid to create a vaccine. And it's antibody independent."

This nasal spray contains a bacteria-based substance called protollin, typically used with other drugs to boost the immune response. Mice treated with the spray have shown a marked reduction in amyloid-beta. Because protollin is already FDA approved, Weiner predicts human trials could get under way as early as 2007.

BWH researchers are also looking at non-vaccine approaches to emptying amyloid-beta from the brain, including enzymes and molecules that appear to either chew the protein up or neutralize its toxic effects. Turning down the amyloid-beta spigot—that is, limiting its production—is the focus of neurology researcher Michael Wolfe, PhD. Armed with a background in medicinal chemistry, he manipulates the biological machinery that produces amyloid-beta. An enzyme called gamma-secretase is his primary target.

Gamma-secretase creates amyloid-beta by cutting a larger protein called amyloid precursor protein, or APP. However, it also cuts a receptor called Notch, which is essential in the development and differentiation of cells throughout life. For this reason, experimental drugs that block gamma-secretase have side effects.

Wolfe, however, believes there is a way around this problem. His team is studying a compound that keeps the enzyme from cutting APP without affecting the cutting of Notch. "It's very exciting because of the potential to block gamma-secretase without the associated toxicities," says Wolfe. "We weren't the first to discover the compound, but we were the first to show how it works on gamma-secretase."

The discovery and the potential of medicinal chemistry have prompted the creation of a new BWH research lab. At the Laboratory for Experimental Alzheimer's Drugs, the mission is to go beyond basic research, prove the compounds work in animal models, encourage pharmaceutical companies to fund clinical trials and get more therapies into patients' hands. "Here in academia, we are aware of the very latest findings," notes Wolfe. "We have a wider perspective with which to judge therapeutic strategies, and it's up to us to prove the principle and pass the baton."

Ultimately, the goal is to reach a point where Alzheimer's disease will be managed akin to heart disease and treated early—before memories are lost. "Someday, a lot of people will be on agents that retard the likelihood of getting the disease," says Selkoe. "And at some point, I think we'll have a lot fewer people suffering from it." ♦

Sources: Dennis Selkoe, MD, Brigham and Women's Hospital; Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging; graphic by Kevin Hand and Karl Gude; ©2004 Newsweek.