Enzyme offers promise of Alzheimer's drugs

The secret is out on beta-secretase, but a patent war may have just begun.

Raising hopes of new drugs for Alzheimer's disease, three companies have announced that they've independently identified this elusive enzyme that helps form the protein deposits that typically fill the brains of people who have the disorder. Scientists also have evidence pointing to a second beta-secretase, one that may help explain why people with Down's syndrome frequently develop Alzheimer's disease.

In Alzheimer's disease, clumps of the protein fragment beta-amyloid clog the brain. Many scientists, but not all, believe that these amyloid plaques kill or damage brain cells, producing memory loss and other symptoms of the illness.

The brain makes beta-amyloid by chopping up a larger molecule, amyloid precursor protein (APP), with enzymes called secretases. Since beta-secretase makes the first cut on APP, scientists predict that drugs blocking its action will reduce the brain's beta-amyloid burden. If amyloid plaques do cause Alzheimer's, then blocking beta-secretase may slow progression of the disease.

"It's a phenomenally important target," says Lennart Mucke of the University of California, San Francisco, who chaired a session on beta-amyloid production at last week's Society for Neuroscience meeting in Miami Beach, Fla.

The first to lay claim to identifying beta-secretase, at least in public, was a group at Amgen in Thousand Oaks, Calif., led by Martin Citron. In the Oct. 22 SCIENCE, the investigators describe a clever genetic approach to finding the enzyme. Drawing on a library of human genes, they added 100 genes at a time to cells until they identified a gene pool that increased the synthesis of beta-amyloid. Sifting through that pool, they homed in on the gene responsible for the elevated amyloid production. As they had hoped, the gene encoded an enzyme that cuts APP at the site where they already knew that beta-secretase works.

At the neuroscience meeting, Sukanto Sinha of Elan Pharmaceuticals in South San Francisco, Calif., revealed that his firm has apparently identified the same enzyme. The investigators purified a protein from human brain tissue that snips APP at the beta-secretase site.

At the same meeting, SmithKline Beecham Pharmaceuticals of King of Prussia, Pa., announced that its scientists, too, had isolated an enzyme identical to that described by Amgen. They will detail their findings in the December MOLECULAR AND CELLULAR NEUROSCIENCE.

While past claims of beta-secretases proved baseless, scientists who study Alzheimer's disease believe that the decade-long search is truly over. "There may be other beta-secretases, but this one fulfills all the criteria," says Michael J. Mullan of the University of South Florida in Tampa.

Identification of additional beta-secretases may come quickly. At the meeting, SmithKline Beecham noted that it has another enzyme with beta-secretase activity. Furthermore, Aleister J. Saunders of Massachusetts General Hospital in Boston and his colleagues have used a simple computer search to find another possible beta-secretase. Using the DNA sequence from the enzyme in Amgen's paper, they scanned a database of previously discovered genes and uncovered one encoding a protein whose amino acid sequence closely resembles Amgen's beta-secretase.

The gene their search identified sits on chromosome 21. That's provocative because people with Down's syndrome, who inherit three copies of chromosome 21, usually develop Alzheimer's disease if they live long enough (SN: 9/20/97, p. 182). Most investigators attribute the link to the third copy of the APP gene, which also resides on chromosome 21, and a resulting increase in amyloid deposits.

Yet mice with an extra copy of a segment of chromosome 16, their equivalent of human chromosome 21, don't develop amyloid deposits despite having an extra APP-gene copy, notes Zygmunt Galdzicki of the Uniformed Services University of the Health Sciences in Bethesda, Md. The mouse chromosome 16 segment might not include the second beta-secretase gene, he speculates. This would suggest that the enzyme is more crucial than APP to the link between Down's syndrome and Alzheimer's disease.

Beta-secretase isn't the only enzyme that investigators have been chasing as a potential target of Alzheimer's drugs. After beta-secretase snips away one end of APP, another elusive enzyme, dubbed gamma-secretase, slices a chunk off the other end to produce beta-amyloid. Over the past few months, Dennis J. Selkoe of Brigham and Women's Hospital in Boston and several other researchers have presented a circumstantial case that a protein called presenilin-1 is a gamma-secretase. Mutations in the gene for presenilin-1 cause early-onset Alzheimer's disease, but it's still not clear how.

In Miami Beach, however, many investigators presented data rejecting an APP-cleaving role for presenilin-1. Todd E. Golde of the Mayo Clinic in Jacksonville, Fla., says, "Most people acknowledge it's a formal possibility, but in their hearts they don't believe it." —*J. Travis*

Y2K problem looms in Hubble repair

Space agency officials have their fingers crossed that the shuttle will roar into space on schedule next month, carrying astronauts who will replace three failed gyroscopes on the Hubble Space Telescope. Already postponed 2 months, the repair mission is critical: If one more of Hubble's six gyroscopes fails, the telescope won't be steady enough to observe the heavens.

There's another reason the space agency hopes the mission won't miss its December launch window and get bumped into next year, SCIENCE NEWS has learned. Because planning time for the Hubble mission was unusually short, NASA hasn't certified that the software the shuttle will use to navigate and rendezvous with Hubble meets year-2000 (Y2K) standards.

The now-infamous Y2K problem stems from the use of two digits instead of four to represent the year in computer programs (SN: 1/2/99, p. 4). Systems continuing to use that shortcut may not know whether 00 means the year 1900 or 2000, creating the potential for serious errors.

Scheduled for launch between Dec. 2 and 14, the 9-day Hubble-repair mission will include four space walks. Although anxious about the schedule, "we have no reason to believe that NASA can't get the mission off on time," says Steven Beckwith, director of the Space Telescope Science Institute in Baltimore, which operates Hubble. If inclement weather or other circumstances force the mission to forgo a December launch, however, the Y2K factor could loom large in efforts to quickly reschedule.

If tests now under way reveal that the NASA software will need only minor modifications to be Y2K-compatible, a postponed mission could fly as early as mid-January. But if the software, essentially the same used to coordinate Hubble repairs in 1997, has to be replaced with a newer version, the

NASA

Scene depicts the upcoming mission to replace failed gyroscopes on Hubble.