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

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

fix could delay the launch by 4 months, says Denny Holt, manager for the Hubble mission at NASA's Johnson Space Center in Houston.

Holt notes, however, that there's only an "outside chance" that the old software would have to be scrapped, causing such a major delay. So far, tests have not uncovered Y2K-related problems. The analysis, however, won't be completed until next month.

Hubble has had only three working gyroscopes since January and another could fail at any time. In announcing plans for the repair mission last March (SN: 3/27/99, p. 203), the agency had pushed for the earliest launch possible, an October date. Wiring problems discovered in the shuttle, however, forced the mission to be rescheduled to December.

In choosing the earliest launch date, the agency hoped to avoid what NASA chief scientist Edward J. Weiler called a "science emergency." Each month that the telescope lies dormant, about $20 million in operational costs would go to waste.

To save time, NASA decided last spring to use the same software that successfully navigated the shuttle during a Hubble repair mission 2 years ago. They had estimated that testing the old software for Y2K problems would have added another 6 months to the planning time, Holt says. If modifying the program now proves necessary, he says, the experience acquired in certifying Y2K compatibility for a newer version of shuttle software should make that task easier. *—R. Cowen*

Chimps outdo people in genetic diversity

If variety is the spice of life, then chimpanzees come loaded with genetic seasoning. Common chimps, with their three subspecies, exhibit far more diversity along a particular stretch of DNA than people do, a new study finds. Moreover, it reveals a surprisingly close genetic connection between common and pygmy chimps.

The results reflect a tight evolutionary relationship, nurtured by frequent interbreeding, among the different chimp groups, report geneticists Svante Pääbo, Henrik Kaessmann, and Victor Wiebe of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany.

Broad genetic consistency among subspecies of these close human relatives supports the notion that chimp groups' unique behaviors in different regions develop through teaching and imitation (SN: 6/19/99, p. 388) rather than through genetic determination, the scientists say.

Until now, genetic studies of chimps have focused on mitochondrial DNA, which is inherited only from the mother. The German team instead studied the X chromosome, which is inherited from both parents. Chemical changes and rearrangements occur rarely in the section examined, thus enhancing efforts to reconstruct ancient evolutionary relationships.

The team determined the chemical arrangement of this DNA segment in 30 common chimps of three subspecies—12 central African chimps, 17 western African chimps, and 1 eastern African chimp. The scientists also tested five members of the pygmy chimp species.

Overall, the common chimps exhibited about four times as much diversity in this genetic region as a group of 70 people did, Pääbo's team reports in the Nov. 5 SCIENCE. Differences between individuals in a single chimp subspecies often exceeded those between common chimps and pygmy chimps.

The two chimp species may thus have taken different evolutionary directions

Chimps' genetic diversity: X chromosome tests mark the spot.

relatively recently, the scientists contend. They calculate that this split occurred about 930,000 years ago. Prior estimates, based on more changeable sections of DNA, had placed the species' division at around 2.5 million years ago.

Further research will examine whether gorillas and orangutans display the abundant diversity of chimps or the narrower genetic range of people, the team says.

The scientists hold that people's relatively low genetic variation has implications for how they evolved. "The simplest explanation is that at some rather recent point in the past, humans were few in numbers," asserts Pääbo. "That point could have been the genetic origin of modern humans."

Pääbo and other researchers have similarly argued, using analyses of mitochondrial DNA, that modern humans arose only about 100,000 years ago. This interpretation of the evidence has proven controversial, however (SN: 2/6/99, p. 88).

Since evolutionary processes have yielded chimp subspecies whereas modern humans fall within a unified species, it's not surprising that chimps harbor more genetic diversity than humans do, remarks geneticist Alan R. Templeton of Washington University in St. Louis.

He adds that lesser human diversity doesn't show, as the German team argues, that a decimated human population in the Stone Age depleted human genetic variation. *—B. Bower*

Soy slows growth of prostate cancers

Men who eat soy-rich diets face a lower risk of deadly prostate cancer, epidemiological studies have indicated. Animal experiments now suggest how soy defends the prostate. The legume induces suicide among cancer cells and limits their spread, scientists report.

In a pair of 6-month-long studies, Göran Hallmans of the University of Umeå in Sweden and his colleagues implanted cancer cells under the skin of rats and hairless mice. Then, they fed the rodents diets deriving one-third of their calories from protein. Some animals got protein from soy, which is rich in plant estrogens known as isoflavones. Whole-grain rye, which contains large amounts of lignans—another family of plant estrogens—provided the protein for others. The final group consumed milk casein, an estrogenfree protein.

Both the soy- and rye-based diets reduced the growth of tumors, compared with the growth of cancers in casein-fed animals. Moreover, only the soy and rye diets induced apoptosis—or natural, programmed death—in the implanted tumor cells, notes coauthor Herman Adlercreutz of the University of Helsinki.

Ordinarily, tumor cells' failure to undergo normal aging and apoptosis contributes to their uncontrolled growth. Adlercreutz says that his team's data represent "the first time it has been shown diet can induce apoptosis."

Jin-Rong Zhou of Harvard Medical School in Boston described related data from mice. His team had placed human cancer cells into the animals' prostates. As tumors began to grow, some mice received diets rich in soy or supplemented with genistein, soy's primary isoflavone. The rest ate casein-based chow.

After 10 weeks, Zhou reports, tumors in casein-fed mice were about twice as big and twice as likely to spread as those in animals fed the soy or genistein.

Zhou notes that most primary cancers aren't lethal; it's their dissemination to other organs that kills. His data indicate that soy retards the cancers' growth and spread at least in part by inhibiting the body's production of blood vessels to supply nutrients to the prostate tumors.

Both Adlercreutz and Zhou reported their findings Monday in Washington, D.C., at the Third International Symposium on the Role of Soy in Preventing and Treating Chronic Disease.

Soy has garnered plenty of media attention for hints that it might cut the risk of breast cancer, says conference chairman Mark Messina, a Port Townsend, Wash., nutritionist. "I think we can now make the case that the prostate data are more impressive," he notes. *—J. Raloff*