Unraveling the Tangled Brain of Alzheimer's

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If you are the sum of accumulated experiences, then Alzheimer's disease is the ultimate thief. The most common of a group of age-related dementias, Alzheimer's disease disrupts the neural system, erasing memories or causing patients to remember things that never happened, changing personality, and destroying the ability to communicate and function before it kills. Alzheimer's disease (AD) affects over 5 million Americans and an estimated 26 million people worldwide.

In 1906, Dr. Alois Alzheimer, a German physician, described the case of Auguste D., a 51 year old patient who suffered mysterious memory loss, disorientation, and odd behavior. Upon her death, Alzheimer autopsied her and discovered that her brain had atrophied. He also found pathological amyloid plaques and neurofibrillary tangles in her brain, but he could not tell whether they were a symptom of her disorder or the cause.

A century later, much about Alzheimer's disease remains an enigma. Most researchers now accept that it is the amyloid β-protein (Aβ) which forms the plaques and fibrils in the Alzheimer's brain that disrupts and kills neurons or triggers a cascade of events that lead to neuronal death. Exactly how Aβ wreaks its havoc is controversial. "We have opinions, but nothing we can put in a textbook," says Dr. David Teplow, professor of neurology at the David Geffen School of Medicine at UCLA.

Four FDA-approved therapies, Aricept, Excelon, Reminyl, and Cognex, are acetylcholinesterase inhibitors. A fifth drug, Namenda, a NMDA receptor antagonist, acts on the glutamatergic neurotransmitter system involved in memory formation and information processing. However, these drugs only help by increasing synaptic communication. "It is as if you are giving aspirin to somebody with pneumonia," said Gal Bitan, Ph.D., assistant professor of neurology at the David Geffen School of Medicine, UCLA. "These drugs help moderately and temporarily but do not prevent the cause of the disease."

Some researchers hypothesize that by the time symptoms appear, the disease has been in progress for 15 years or so, but diagnoses based on biomarkers have emerged only recently. Aβ, a 40–42 amino acid, is produced in the brains of healthy people and its role is unknown. Normally, Aβ is cleaved from an amyloid precursor protein (APP) by β and γ secretase enzymes and further metabolized. But in AD, the Aβ accumulates and self assembles, first into soluble oligomers and then into insoluble plaques in the brain, causing nerve injury, inflammation, and cholinergic deficits that impair nerve communication and eventually destroy neurons.

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According to Bitan, soluble Aβ oligomers are the proximal causes of these insults and later go on to form the offending fibrils and plaques. "So what we believe today, what happens in Alzheimer's, is that in the very early stages, these oligomers—even before they kill the neurons—disrupt their ability to talk with each other," said Bitan. "And therefore you lose your memory."

Loitering in Risky Genetic Neighborhoods

AD stems from the interplay of heredity and lifestyle. A form of aggressive, early-onset AD that strikes less than 1% of people before age 65 is attributed to mutations in the amyloid precursor protein (*APP*) and presenilin-1 and presenilin-2 genes.

But for most people, getting old is the main factor that raises risk for AD, as well as prior head trauma and a history of depression. The common apolipoprotein E (*ApoE*) gene, which is located on chromosome 19 and involved in lipid and triglyceride transport, is implicated in AD. One allele in particular, ε4, raises the risk of developing Alzheimer's disease 3-fold over the general population if you have one copy, and 15-fold if you have two.

"There are a lot of diseases that have a genetic component, but in many of them, if not most of them, the genetic component causes only a minority of the cases," said Teplow. "The major caseload comes from nongenetic reasons or at least genetic reasons that have not been identified yet. It is true in Alzheimer's disease. It is true in the prion diseases. It is true in amyotrophic lateral sclerosis (ALS). It is true in Parkinson's. All these neurodegenerative diseases are diseases of aging, and the minority of them are caused by identifiable genetic changes. So Aβ may or may not be the cause."

New drugs inching closer to the clinic promise to delay or stop the progression of the disease, but there is no single path forward. A number of companies, including Myriad, Wyeth, Elan, and Glaxo, have compounds in phase III testing that either block the production of Aβ, attempt to eliminate fibrils, or affect assembly of existing Aβ.

Blocking Amyloid Production

South San Francisco/Oklahoma City-based CoMentis (http://www.comentis.com) is developing a β secretase inhibitor, CTS-21166, which has just finished phase I trials.

"Our company is targeting one of the most attractive targets, the β secretase enzyme, in the brain and coming up with an inhibitor of that enzyme would reduce the production of Aβ 40–42." said Dr. W. Scott Harkonen, president and CEO of CoMentis. According to Harkonen, β secretase is a "pretty clean target," but γ secretase is associated with more serious

side effects. CoMentis developed its small-molecule drug using crystallography-based rational drug design. Scientific founders Jordan Tang, Ph.D. and colleagues at Oklahoma Medical Research Foundation and Arun Ghosh, Ph.D., now at Purdue University, were among the first to isolate the secretases and developed the first inhibitor of β secretase. "We've been able to come up with a family of orally available compounds that get into the brain and have single-digit nanomolar potency," said Harkonen.

"The problem is that with some of these inhibitors, especially the γ inhibitors, is that γ secretase not only cuts APP but other molecules as well," said Teplow. "If you inhibit this enzyme, you can potentially get other significant side effects."

Perhaps the furthest along is Myriad Pharmaceutical's (http://www.myriad.com) Flurizan, a γ secretase modulator now in dual phase III trials for patients with mild Alzheimer's disease. Flurizan is a selective amyloid-lowering agent (SALA). The drug so far has lowered levels of Aβ 42 in vitro and in animals.

"On Flurizan, there is a debate as to whether it will be potent enough to really make a difference in slowing Alzheimer's symptoms," said Dr. Dennis Selkoe, Coates Professor of Neurology at Harvard Medical School and codirector of the Center for Neurologic Diseases at Brigham and Women's Hospital. Selkoe was a founding scientist of Athena Neurosciences, now Elan Pharmaceuticals (http://www.elan.com). "My view is that it might be. I think the way they've designed the trial is very good. I think we will know mid-2008 or a little later whether it has had a clinical benefit or not."

Preventing Assembly

Toronto-based Transition Therapeutics (http://www.transitiontherapeutics.com) has a codevelopment deal with Elan worth potentially $200 million in milestone payments ($15 million upfront) for its oral small-molecule drug ELND005 (formerly AZD-103). Its compound, a scyllo-inositol, received fast-track designation from the FDA. "The idea with this compound is that it can be preventative if you can get it early enough to prevent those fibrils from forming, but if you have existing fibrils, it can break those fibrils down," said Dr. Tony Cruz, Transition Therapeutics CEO. According to Cruz, the compound enters the brain via the myo-inositol transporter. So far, it has increased survival in transgenic animal models. "It has a very good safety profile, so we can go at very high doses in humans without fear of major adverse events." Elan and Transition are currently enrolling 340 patients with mild-to-moderate Alzheimer's disease in an 18 month phase II efficacy trial in North America. "It is a natural product," said Dennis Selkoe. "But it has to be given in very high doses in order to achieve useful brain levels. So one doesn't yet know if it is going to be efficacious enough."

The compound was licensed from the work of Professor JoAnne McLaurin and colleagues at the Centre for Research in Neurodegenerative Diseases at the University of Toronto, who identified a small molecule, scyllo-cyclohexanehexol, that prevented the Aβ peptide from aggregating in fibrils by stabilizing it in a low molecular weight.

Clearing Out Amyloid Proteins

Elan and Wyeth's AAB-001(Bapineuzumab) is a humanized monoclonal anti-Aβ antibody intended to bind and remove the Aβ peptide that accumulates in the brain. This vaccine is based on the work of Dale Schenk, Ph.D., executive vice president at Elan. The company is enrolling 41,000 patients in North America and Europe in a phase III clinical test overlapping with a phase II study. The trial will have four arms; two of those will be comprised of people who possess the *APOε4* allele and two will comprise people who do not. "I think this is the first actual trial where a specific genotype is the basis for putting people into two parallel trials," said Selkoe. According to Selkoe, it is possible that the drug will work better in people without the *APOε4* variants because they have a less aggressive form of Alzheimer's and tend not have as much vascular amyloid. Eli Lilly also has a competitive antibody in phase II and a more traditional γ secretase inhibitor.

More Questions than Answers

Elan is also actively vaccinating Alzheimer's patients with an Aβ peptide. The original idea of using the immune system to fight Alzheimer's disease came from Professor Beka Solomon's lab at Tel Aviv University. Vaccinating transgenic mice against components of human amyloid showed Aβ clearance and recovery of memory, but Elan and Wyeth aborted a phase II human trial of AN 1792 in 2002 when 6% of patients developed autoimmune encephalitis, a severe inflammation of the brain. "There was a correlation with their antibody titers and their mental status," said Selkoe. "The earlier active vaccine will never be used again, but Elan and Wyeth are developing a truncated Aβ peptide without the t-cell epitope, ACC-001, now in phase II."

David Teplow often refers to a comment made to his wife, Arden, a clinical therapist, by an early stage Alzheimer patient who described her increasing confusion as "I don't know what I know." Teplow says, "And that is just a chilling comment for me and for other people also. It reflects part of the clinical presentation which causes quite tremendous anxiety in the early stages of the disease. It is that sense of cognitive disorientation that is really very devastating to many people."

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