Experimental Alzheimer Drugs Targeting Beta-Amyloid and the “Amyloid Hypothesis”

In Alzheimer’s disease, brain cells that process, store and retrieve information degenerate and die. Although scientists do not yet know the underlying cause of this destruction, they have identified several possible culprits.

One prime suspect is a microscopic protein fragment called beta-amyloid (BAY-tuh AM-uh-loyd). Some researchers believe flaws in processes governing production, accumulation, or disposal of beta-amyloid are the primary cause of Alzheimer’s. This theory is called “the amyloid hypothesis.”

What is beta-amyloid?
Beta-amyloid is a small piece of a larger protein called “amyloid precursor protein” (APP). Although scientists have not yet determined APP’s normal function, they have learned a great deal about how it appears to work. In its complete form, APP extends from the inside to the outside of brain cells by passing through a fatty membrane around the cell. When APP is “activated” to do its normal job, it is cut by other proteins into smaller sections that stay inside and outside cells. There are several different ways APP can be cut. Under some circumstances, one of the pieces produced is beta-amyloid.

Why is beta-amyloid a prime suspect in Alzheimer’s disease?
Beta-amyloid is chemically “stickier” than other fragments produced when APP is cut. It accumulates by stages into microscopic amyloid plaques that are considered one hallmark of brains affected by Alzheimer’s. The pieces first form small clusters called oligomers (AWL-igg-uh-merz), then chains of clusters called fibrils, then “mats” of fibrils called beta-sheets. The final stage is plaques, which contain clumps of beta-sheets and other substances.

According to the amyloid hypothesis, these stages of beta-amyloid aggregation disrupt brain cells by clogging points of cell-to-cell communication, activating immune cells that trigger inflammation and devour disabled cells, and, ultimately, killing cells.

What evidence implicates beta-amyloid?
Supporters of the amyloid hypothesis cite three main lines of evidence:

1. In a few hundred extended families worldwide, scientists have identified rare genes that virtually guarantee an individual will develop Alzheimer’s. All of these genes increase production or accumulation of beta-amyloid.
2. Scientists have developed mice genetically engineered to carry some of the human genes associated with rare forms of inherited Alzheimer’s. The mice develop amyloid plaques as well as difficulty remembering their way through mazes and other symptoms that mimic human Alzheimer’s.
3. Individuals with Down syndrome, who have three copies of the chromosome carrying the APP gene instead of the normal two, almost invariably develop amyloid plaques and symptoms of Alzheimer’s disease, usually by middle age.
Not all scientists are convinced that beta-amyloid is the primary cause of Alzheimer’s. Researchers worldwide are investigating a variety of other possible triggers for the destructive series of events that eventually kills brain cells.

**If beta-amyloid does play an important role, how could treatments block its effects?**

Scientists are exploring a number of strategies to block the effects of beta-amyloid. Several drugs targeting beta-amyloid have reached human clinical trials, but there is not yet any clear indication that these drugs can improve Alzheimer symptoms or protect brain cells. Some animal studies have suggested that anti-beta-amyloid drugs can reduce brain amyloid levels and improve memory problems in aging mice genetically engineered to develop symptoms similar to Alzheimer’s disease.

Experimental strategies focusing on beta-amyloid aim to decrease the production of beta-amyloid; prevent the aggregation of beta-amyloid; or increase the removal of beta-amyloid from the brain.

**Decreasing beta-amyloid production**

To decrease beta-amyloid production, experimental drugs change the behavior of proteins that cut APP into beta-amyloid. Scientists have identified several proteins called secretases (SEE-kruh-tay-sez) that are involved in cutting APP into beta-amyloid. Changing the behavior of these proteins could prevent or reduce beta-amyloid production. Drugs called “secretase inhibitors” block the clipping action of secretases. One such drug in phase III clinical trials is LY-450139, a gamma-secretase inhibitor. LY-450139 has been shown to reduce beta-amyloid concentration in blood and cerebrospinal fluid. Beta-secretase inhibitors are also in development.

Another approach reduces beta-amyloid by changing (“modulating”) the way secretases work or encouraging (“activating”) the functioning of secretases such as alpha-secretase that cut APP into fragments other than beta-amyloid. R-fluriprofen (Flurizan®), a promising gamma-secretase modulator, failed Phase III trials in mid-2008, but scientific investigations into secretase modulators continue.

**Preventing beta-amyloid aggregation**

Because Alzheimer’s is characterized by amyloid plaques, scientists have explored drugs that prevent beta-amyloid aggregation as a potential treatment for Alzheimer’s. One such experimental drug in Phase II trials is PBT2, which is designed to inhibit formation of oligomers. A Phase III trial of Tramiprosate (Alzhemed®), designed to block aggregation of beta-amyloid into plaques, was halted in late 2007 due to high data variations among trial sites that invalidated the statistical model for evaluating the drug. The clinical trial was carried out at 67 sites and involved 1,052 individuals with Alzheimer’s.

Some scientific studies suggest that the toxic effects of beta-amyloid occur before the formation of plaques and oligomers. Research is under way to better understand the potential role of the aggregation of very small amounts of beta-amyloid — smaller than the amount in oligomers — in the development of Alzheimer’s.
**Increasing beta-amyloid removal**

Methods to increase removal of beta-amyloid from the brain include mobilizing the immune system to produce antibodies to attack beta-amyloid; administering laboratory-produced antibodies to beta-amyloid; and administering natural agents with anti-amyloid effects.

**Immune system–generated antibodies to attack beta-amyloid**

Experimental agents in this category are called “active vaccines.” ACC-001 is an example of an active vaccine in clinical trials. The Phase II drug incorporates a beta-amyloid fragment that is attached to a carrier protein. When injected, it is expected that the body will produce antibodies to beta-amyloid. Researchers hope that the antibodies will attack beta-amyloid and reduce beta-amyloid levels in the brain. The technology used to make ACC-001 has been used in some pediatric vaccines.

An earlier active vaccine, AN-1792, showed promise in animal studies, but human clinical trials of the drug were stopped when some study participants developed brain inflammation. Final results of the study showed that, overall, vaccine recipients fared no better than those who received a placebo. However, vaccine recipients who developed the highest levels of antibodies against beta-amyloid declined less, on average, in tests of mental function and in some cases showed improved performance compared with recipients who developed lower levels of antibodies.

**Laboratory-produced antibodies to beta-amyloid**

Experimental drugs in this category are called “passive vaccines.” These vaccines may be safer because they can be given in predetermined doses and do not stay in the body after dosing ends. The humanized monoclonal antibody AAB-001 (bapineuzumab) is an example of a passive vaccine being tested for Alzheimer’s. In Phase III clinical trials at sites across the world, AAB-001 is designed to bind to and remove beta-amyloid from the brain. AAB-001 has been given the “fast track” designation by the U.S. Food and Drug Administration. This designation is intended to facilitate the development and expedite review of drugs that treat serious or life-threatening conditions and may address unmet medical needs.

**Natural agents with anti-amyloid effects**

Intravenous immunoglobulin (IVIg) contains natural antibodies to amyloid that may reduce beta-amyloid levels. Now in clinical trials, IVIg is obtained from the plasma of human blood donors. In a small Phase I study, cognitive decline stopped after six months of therapy in all participants who received IVIg. The vast majority of patients saw improvement in cognitive function.

The Alzheimer’s Association is the leading voluntary health organization in Alzheimer care, support and research.

**Updated** June 2008