

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 the Alzheimer brain. 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 include the following:

1. Mobilize the immune system to produce anti-bodies to “recognize” and “attack” beta-amyloid. AN-1792, an experimental “vaccine” based on this principle, showed promise in animal studies, but researchers stopped human clinical trials after some vaccine recipients developed serious brain inflammation. It is difficult to assess the vaccine's effect because the trial stopped before participants received all their planned doses, but scientists note some encouraging preliminary signs.

Several autopsies have been performed on enrollees who later died of causes unrelated to the trial, and their brains appear to have fewer amyloid deposits than would be expected. Final results of the trial, published in May 2005, show that vaccine recipients fared no better than those who took the placebo on the trial's chief tests of memory, thinking and overall function. However, vaccine recipients who developed the highest levels of antibodies against beta-amyloid declined less in their average performance on an additional battery of nine tests of mental function and their scores actually improved slightly on a few of the specific tests.

One puzzling result of the AN-1792 trial has not yet been explained: participants who developed high levels of beta-amyloid antibodies tended to experience greater brain shrinkage. Over time, the brain of an individual with Alzheimer's shrinks dramatically. An effective treatment would be expected to prevent or reduce shrinkage.

Overall, many scientists consider the AN-1792 results promising enough to justify further investigation of anti-amyloid immunization. Researchers are exploring several alternative ways to mobilize the immune system without triggering dangerous inflammation.

2. Administer laboratory-produced antibodies to beta-amyloid. One possible way to make a safer vaccine might be to administer laboratory-produced antibodies instead of mobilizing the immune system to produce its own. Antibodies developed in the laboratory can be given in predetermined doses like any other drug and do not persist in the body after

dosing stops. Several companies, including Elan, are developing laboratory engineered antibeta-amyloid antibodies.

3. Change the behavior of the 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. Other approaches reduce beta-amyloid by changing the way secretases work or encouraging the activity of secretases that cut APP into fragments other than beta-amyloid. One example of a drug that may reduce beta-amyloid by changing the way a secretase works is R-flurbiprofen (Flurizan), under development by Myriad Pharmaceuticals.

4. Block accumulation of beta-amyloid. Since beta-amyloid exists in multiple forms in the Alzheimer brain, one unanswered question is which form might be the most toxic. If some early stage of accumulation is the most damaging, one treatment approach might be to prevent the individual fragments from sticking together. Drugs in this class are called “anti-aggregants.” The first large, Phase III clinical trial of an anti-aggregant (NC-758 or Alzhemed) was launched in August 2004. In August of 2007, the U.S. Food and Drug Administration (FDA) deemed the U.S. Alzhemed trial results inconclusive. A European phase III clinical trial of the drug is ongoing.

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

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