Treatment Horizon

Alzheimer´s Association, July 3, 2018

A worldwide quest is under way to find new treatments to stop, slow or even prevent Alzheimer's disease. Because new drugs take years to produce from concept to market — and because drugs that seem promising in early-stage studies may not work as hoped in large-scale trials — it is critical that Alzheimer's and other dementia research continues to accelerate. To advance this effort, the Alzheimer's Association funds researchers looking at new treatment strategies and advocates for more federal funding of Alzheimer's research.

The hope for future drugs

Currently, there are five Alzheimer's drugs approved by the U.S. Food and Drug Administration (FDA) that treat the symptoms of Alzheimer's disease — temporarily helping memory and thinking problems — with a sixth drug available globally. However, these medications do not treat the underlying causes of the disease.

Many of the new drugs in development aim to modify the disease process itself by impacting one or more of the wide-ranging brain changes that Alzheimer's causes. These changes offer potential "targets" for new drugs to stop or slow the progress of the disease. Many researchers believe successful treatment will eventually involve a "cocktail" of medications aimed at several targets, similar to current state-of-the-art treatments for many cancers and AIDS.

Targets for future drugs

Over the last 30 years, researchers have made remarkable progress in understanding healthy brain function and what goes wrong in Alzheimer's disease. The following are examples of promising targets for next-generation drug therapies under investigation in current research studies:

Beta-amyloid

The chief component of plaques, beta-amyloid is a hallmark of Alzheimer's. Scientists now have a detailed understanding of how this protein fragment is clipped from its parent protein, amyloid precursor protein (APP), by two enzymes — beta-secretase and gamma-secretase — to form the beta-amyloid protein present in

abnormally high levels in the brains of people with Alzheimer's. Researchers are developing medications aimed at almost every point in amyloid processing. This includes blocking activity of the beta-secretase enzyme; preventing the beta-amyloid fragments from clumping into plaques; and even using antibodies against beta-amyloid to clear it from the brain.

Current drug in research that targets beta-amyloid: Aducanumab

Aducanumab is a recombinant monoclonal antibody targeting aggregated forms of beta-amyloid, such as oligomers and fibrils, that can develop into amyloid plaque in the brains of people with Alzheimer's disease. Early studies showed decreased levels of beta-amyloid in the brains of study volunteers. Two phase 3 studies are under way to test whether monthly doses of aducanumab can slow cognitive and functional decline in people with early Alzheimer's disease. The studies are expected to be completed in late 2019 and late 2020. (Drug is still in research; not available to the public.)

Beta-secretase (BACE)

One of the enzymes that clips APP, BACE makes it possible for beta-amyloid to form. Therapies that interrupt this process may reduce the amount of beta-amyloid in the brain and ultimately intervene in the development of Alzheimer's disease.

Current drug in research that targets beta-secretase: JNJ-54861911

JNJ-54861911 inhibits the ability of the beta-secretase enzyme to make beta-amyloid. It is currently in two phase 3 studies to determine if it slows cognitive decline in people who do not have Alzheimer's symptoms but do have elevated levels of beta-amyloid in the brain. The studies are expected to be completed in fall 2023 and spring 2024. JNJ-54861911 is administered in pill form. (Drug is still in research; not available to the public.)

Tau protein

The chief component of tangles, tau protein is another hallmark of Alzheimer's. Tau protein helps maintain the structure of a neuron, including tiny tube-like structures called microtubules that deliver nutrients throughout the neuron.

Current drug in research that targets tau protein: AADvac1

AADvac1 is a vaccine that stimulates the body's immune system to attack an abnormal form of tau protein that destabilizes the structure of neurons. If successful, it has the potential to help stop the progression of Alzheimer's disease. A phase 2 clinical trial enrolling 208 volunteers with mild Alzheimer's disease began in March

2015 and is expected to be completed in summer 2019. (Drug is still in research; not available to the public.)

Inflammation

Inflammation in the brain has long been known to play a role in the changes that occur in Alzheimer's disease. Both beta-amyloid plaques and tau tangles cause an immune response in the brain, and microglia cells act as the first form of immune defense against them. However, while microglia help clear beta-amyloid in the brain, they can become overactive in the presence of plaques and produce compounds that damage nearby cells.

Current drug in research that targets inflammation: Sargramostim

Approved by the FDA for bone marrow stimulation in people with leukemia, sargramostim stimulates the innate immune system. It is being tested in Alzheimer's because it may stimulate immune processes that could protect neurons in the brain from toxic proteins. A phase 2 study of sargramostim is underway. It is expected to be completed in late 2018. (Drug is still in research; not available to the public.)

5-HT2A receptor

The 5-HT2A receptor is found on the surface of many neurons that are involved with awareness and thinking. Molecules of the neurotransmitter serotonin fit into 5-HT2A receptors as a key fits into a lock. When this happens, the 5-HT2A-containing neurons communicate more with their neighboring neurons. Overactive communication between neurons, however, may play a role in dementia-related psychosis.

Current drug in research that targets 5-HT2A: Pimavanserin

Pimavanserin is an inverse agonist for the 5-HT2A receptor. This means that pimavanserin mimics the shape of the serotonin "key" and fits into the 5-HT2A "lock." However, pimavanserin has the opposite effect of serotonin: it reduces communication between neurons. This may have the effect of reducing the symptoms of dementia-related psychosis. A phase 3 clinical trial of pimavanserin is underway. The study is expected to be completed in spring 2020. (Drug is still in research; not available to the public.)

Alzheimer's prevention trials

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study

The A4 Study is examining the effectiveness of solanezumab, a drug targeting beta-amyloid, in 1,150 symptom-free volunteers whose positron emission tomography (PET) scans show abnormally high levels of beta-amyloid in the brain. High levels of

beta-amyloid in the brain increase the risk for developing Alzheimer's disease. Researchers hope that early intervention in individuals at increased risk of developing Alzheimer's will prevent cognitive decline.

Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU)

Mutations on three genes are known to cause a rare form of Alzheimer's disease that accounts for less than 1 percent of cases. When a person has one of these mutations, he or she has a 95 to 100 percent chance of developing Alzheimer's. DIAN-TU hopes to slow or stop the development of Alzheimer's in these individuals with experimental drugs. Two drugs, gantenerumab and solanezumab, are currently being tested. Both are designed to help remove excess beta-amyloid in the brain. The brain changes of people with this form of Alzheimer's are very similar to the brain changes of those with the more common sporadic form of Alzheimer's disease. It's possible that a drug that slows or stops Alzheimer's in DIAN-TU participants will also slow or stop Alzheimer's in people with or at high risk of sporadic Alzheimer's.

The Alzheimer's Prevention Initiative (API)

API includes both the Autosomal Dominant Alzheimer's Disease (ADAD) trial and the Generation Study. Like DIAN-TU, the ADAD trial tests therapies in people who have a gene mutation that causes Alzheimer's, but who have not yet developed symptoms. Drugs that delay or prevent symptoms in people with genetic mutations for Alzheimer's may potentially delay or prevent symptoms in people with the brain changes of Alzheimer's who do not have these genetic mutations. The ADAD trial is studying the effects of crenezumab, an immune-based therapy. Crenezumab delivers antibodies against beta-amyloid in an effort to reduce the negative cognitive effects of excess beta-amyloid. The Generation Study includes cognitively healthy older adults who are at high risk of developing Alzheimer's based on their age and having two copies of the Alzheimer's risk gene APOE-e4. This study focuses on whether two investigational drugs — an active immunotherapy (CAD106) and a BACE inhibitor (CNP520) — can prevent or delay the onset of Alzheimer's symptoms.

Participate in a clinical trial

If you are interested in participating in a current clinical trial, use Alzheimer's Association TrialMatch®, a free, easy-to-use clinical studies matching service that generates customized lists of studies based on user-provided information. A lack of volunteers for Alzheimer's clinical trials is one of the greatest obstacles slowing the progress of potential new treatments.

Related information

- How Clinical Trials Work
- Why Participate in a Clinical Trial?