Alzheimer’s disease: Treatment horizons

The U.S. Food and Drug Administration (FDA) has approved six drugs to treat the symptoms of Alzheimer’s disease:

- Galantamine (Razadyne®)
- Rivastigmine (Exelon®)
- Donepezil (Aricept®)
- Tacrine (Cognex®)
- Memantine (Namenda®)
- Memantine + Donepezil (Namzaric®)

These drugs work by increasing the amount of chemicals in the brain called neurotransmitters, which help nerve cells in the brain (neurons) communicate with each other. While these drugs help with symptoms to various degrees of effectiveness across populations, they do not treat the underlying causes of Alzheimer’s or slow its progression.

Targets for future drugs

Many of the drugs in development aim to interrupt the disease process itself by impacting one or more of the brain changes caused by Alzheimer’s. These changes offer potential "targets" for new drugs to slow or stop the progress of the disease. Researchers believe successful treatment will eventually involve a combination of medications aimed at several targets, similar to current treatments for many cancers and AIDS.

The following are examples of promising targets for next-generation drug therapies under investigation in current research studies.

Target: Beta-amyloid

**Beta-amyloid** is the chief component of plaques, one hallmark Alzheimer’s brain abnormality. Scientists now have a detailed understanding of how this protein fragment is clipped from its parent compound, amyloid precursor protein (APP), by two enzymes — beta-secretase and gamma-secretase — to form the beta-amyloid protein that is present in abnormally high levels in the brains of people with Alzheimer’s.

Researchers are developing medications aimed at virtually every point in the amyloid processing pathway. 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. Several clinical trials of investigational drugs targeting beta-amyloid are under way.

Current drug in research that targets beta-amyloid: Solanezumab

Solanezumab is a monoclonal antibody designed to lower the level of beta-amyloid in the brain. These antibodies bind to beta-amyloid, preventing the formation of plaques; solanezumab may also help carry excess beta-amyloid away from the brain. Several studies of this drug are under way with the goal determining if solanezumab improves
participants’ cognition (thinking and memory) and functioning. Some participants will undergo a brain scan called positron emission tomography (PET) to determine levels of beta-amyloid in the brain. (Drug is still in research; not available to the public.)

Target: Beta-secretase

**Beta-secretase (BACE)** is one of the enzymes that clips APP and 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: MK-8931**

MK-8931 is a BACE inhibitor — it inhibits the ability of the beta-secretase enzyme to make beta-amyloid. At the Alzheimer’s Association International Conference® 2013 (AAIC®), researchers reported that the drug significantly lowered beta-amyloid levels in people with mild-to-moderate Alzheimer’s. MK-8931 is being tested in two phase 3 clinical trials. (Drug is still in research; not available to the public.)

Target: Tau protein

**Tau protein** is the chief component of tangles, the other hallmark brain abnormality of Alzheimer’s disease. Tau protein helps maintain the structure of a neuron, including tiny tube-like structures called microtubules that deliver nutrients throughout the neuron. Researchers are investigating mechanisms to prevent tau protein from collapsing and twisting into tangles, a process that destroys microtubules and, ultimately, the neuron itself.

**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. At AAIC 2015, researchers reported that AADvac1 was safe and well tolerated by participants in a phase 1 clinical trial. (Drug is still in research; not available to the public.)

Target: Inflammation

**Inflammation** is another key Alzheimer’s brain abnormality. Both beta-amyloid plaques and tau tangles cause an immune response in the brain. Microglia are cells that act as the first form of immune defense in the brain. While microglia help clear beta-amyloid in the brain, they may become overactive in the presence of beta-amyloid and produce compounds that damage nearby cells.

**Current drug in research that targets inflammation: CSP-1103**

CSP-1103 is a microglial modulator that aims to reduce inflammation in the brain. At AAIC 2013, researchers presented the results of a 90-week trial in which people who
had mild cognitive impairment (MCI) were given CSP-1103. Preliminary studies showed that CSP-1103 prevented beta-amyloid from being deposited on neurons and forming plaques. It also reduced problems with thinking and memory (cognition). The cognitive tests of people who had participated for at least 64 weeks showed statistically significant improvements in participants’ cognitive abilities. (Drug is still in research; not available to the public.)

**Target: Insulin resistance**

*Insulin resistance* in the brain is another common feature of Alzheimer’s disease. For reasons researchers do not completely understand, the brain becomes resistant to the normal effects of insulin, including the conversion of glucose to energy that brain cells can use to fuel cell functioning. Some research suggests that beta-amyloid decreases the body’s ability to use insulin. Other research has found reduced levels of insulin in the brain.

**Current drug in research that targets insulin resistance: Intranasal insulin**

Intranasal insulin is a therapy being tested in multiple studies for its effects on memory, thinking and daily functioning in people with MCI and mild-to-moderate Alzheimer’s disease. There is growing evidence that insulin plays an important role in keeping the brain healthy. Intranasal administration of insulin may help by increasing insulin signaling in the brain. (Drug is still in research; not available to the public.)

**Alzheimer’s disease prevention trials**

*The Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) Trial*
The A4 trial is studying the effectiveness of solanezumab, a drug targeting beta-amyloid, in 1,150 symptom-free volunteers whose 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 the cognitive decline of this devastating and ultimately fatal disease.

*TOMMORROW Trial*
The TOMMORROW Trial includes 3,500 asymptomatic individuals, some of whom have the Alzheimer’s risk gene apolipoprotein E e4 (APOE-e4) or the TOMM40 risk gene. The trial will explore whether the anti-diabetes drug pioglitazone can prevent mild cognitive impairment due to Alzheimer’s disease. Studies suggest that pioglitazone may decrease inflammation and beta-amyloid levels in the brain, improve blood flow to the brain and increase the brain’s ability to use glucose to fuel nerve cells.

*Dominantly Inherited Alzheimer Network Trial 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 percent to 100 percent chance of developing Alzheimer’s. DIAN TU tracks changes in the brains of people with those rare Alzheimer’s gene mutations who have not yet developed the disease. In addition, researchers are studying two drug candidates (gantenerumab and
solanezumab) that may slow or stop brain changes and prevent symptoms like memory loss from occurring.

**The Alzheimer’s Prevention Initiative (API)**
Like DIAN TU, API tests therapies in people who have a gene mutation that causes Alzheimer’s, but 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 API 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.

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