CLOSING IN ON ALZHEIMER’S DISEASE

Knowledge about the neuropathology of Alzheimer’s disease has blossomed over the past few decades, leading to a better understanding of the condition and new ways to attack it. By Dawn Connolly.

PATHOLOGY

Alzheimer’s disease is a progressive disorder. After symptoms first appear, life expectancy is around 8-10 years. Memory is typically the first problem, then difficulties with cognition and planning become marked, speech and language are affected, and patients may experience altered personality and behavior. Eventually, individuals are unable to care for themselves.

Two main processes are thought to drive degeneration: intracellular accumulation of a protein called tau and extracellular deposition of a protein called beta-amyloid (Aβ), leading to formation of neurofibrillary tangles and amyloid plaques. Although most people develop some tangles and plaques as they age, those with symptoms of Alzheimer’s disease tend to develop far more.

OLIGOMERS

Oligomers are thought to be more damaging than plaques because they block cell-to-cell signaling at synapses and may also activate immune system cells triggering an attack.

Inside the healthy neuron, parallel microtubules provide the cell’s transport system for nutrition and key materials to be delivered. Tau protein act as scaffolding for the cell’s transport system for nutrition and key materials to be delivered. Tau protein act as scaffolding for the cell’s transport system for nutrition and key materials to be delivered. Tau protein act as scaffolding for the cell’s transport system for nutrition and key materials to be delivered. Tau protein act as scaffolding for the cell’s transport system for nutrition and key materials to be delivered. Tau protein act as scaffolding for the cell’s transport system for nutrition and key materials to be delivered.

Neurofibrillary tangles form within nerve cells, while amyloid plaques build up in spaces between the nerve cells.

BIological targets

Licensed drugs treat symptoms by regulating levels of the neurotransmitters acetylcholine and glutamate, which are important for neuronal communication. In contrast, goals in development aim to inhibit the mechanisms that lead to the buildup of plaques and tangles characteristic of the condition by targeting Aβ, tau or the inflammation caused by plaques and tangles.

Monoclonal antibodies, such as Merck’s T3D-959, are a humanized monoclonal G2f antibody that recognizes soluble forms of Aβ, not fibrils. It stimulates microglia to clear amyloid plaques. Biogen’s aducanumab is a high affinity, fully human IgG1 antibody, which recognizes soluble monomers of Aβ. It inhibits BACE1, to interfere with production of Aβ.

MEMantine

Memantine, a N-methyl-D-aspartate (NMDA) glutamate receptor agonist, which has the potential to inhibit both the Aβ and tau pathways.

Solanezumab, an immunoglobulin G1 antibody that selectively binds to large, soluble Aβ protofibrils and stimulates their clearance by microglial cells.

FEATURE

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Drug development

Alzheimer’s disease (AD) was first identified by German doctor Alois Alzheimer in 1906, but it wasn’t until 1993 that the first drug to target the symptoms of Alzheimer’s was approved by the US Food and Drug Administration (FDA). Despite a 99.6% attrition rate for AD drugs between 2002 and 2012, there is hope for current pipeline drugs being tested in prodromal and mild AD with this aim of stopping disease development rather than treating symptoms.

1993: Warner-Lambert’s tacrine (Cognex) receives FDA approval for mild-to-moderate AD, but poor acceptance.

1999: Elan’s crenezumab (Crenezumab) receives FDA approval for mild-to-moderate AD. This trial showed a benefit on cognition.

2006: Pfizer’s tanezumab (Tanezumab) receives FDA approval for mild-to-moderate AD.

2009: Shionogi’s galantamine (Reminyl) receives European Medicines Agency (EMA) approval for mild-to-moderate AD.

2012: Two phase 3 trials of Eli Lilly’s monoclonal antibody Aducanumab begin recruiting 1800 people with early-stage AD. Estimated completion date is July 2018.

2013: Phase II trial of Biogen/EliLilly’s monoclonal antibody BAN2401 begins recruiting 800 people with early-stage AD. Estimated completion date is July 2018.

2016: Two phase trials of TauRx Therapeutics’ LMTX, a second-generation tau aggregation inhibitor, begin in patients with prodromal and mild-to-moderate AD. Study results are expected in 2020.

2019: Phase II trial of Genentech’s monoclonal antibody gantenerumab (tanzeumab) in patients with prodromal AD, with results due in 2020. Two additional phase 2 trials in mild-to-moderate AD are ongoing.

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2014: Actua’s Anti-MK1067 monoclonal antibody combination product shows promising results for both prodromal and mild-to-moderate AD.

2015: Takeda pharmaceuticals reports a dose-dependent reduction in amyloid plaques and slowing of cognitive decline in phase 2 trials of MK-8931, an antibody that reduces soluble Aβ. A phase 3 trial compared with placebo is planned for patients with mild-to-moderate AD.

2018: Anti-Aβ (soluble/insoluble) monoclonal antibody combination product shows promise in a phase II trial for moderate-to-severe AD.

2018: Amylone Pharmaceuticals and Omega-3 drug combination shows promise in a phase II trial for moderate-to-severe AD.

2019: Phase III trial of Merck’s TACE inhibitor MK-8931, a dual nuclear receptor agonist, which has the potential to inhibit both the Aβ and tau pathways.

2019: Phase III trial of Pfizer’s solanezumab, an immunoglobulin G1 antibody that selectively binds to large, soluble Aβ protofibrils and stimulates their clearance by microglial cells.

Phase II trial of Biogen/EliLilly’s monoclonal antibody BAN2401 begins recruiting 800 people with early-stage AD. Estimated completion date is July 2018.

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