

# Structural analysis of relevant drug targets for Alzheimer's disease

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Alzheimer's Disease (AD) is classified as a neurodegenerative non-curable disease that affects millions worldwide. Current drugs have side effects that are significant. In AD, the beta-amyloid precursor protein ( $\beta$ -APP) that is critical for normal neuronal growth, survival and repair, is improperly cleaved by specific aspartic proteases, which create fragments that form plaques of amyloid beta. These fragments aggregate outside neurons and create plaques which lead to destruction of neural signaling. The pathophysiology of AD is complex, although there are many approaches to combat the disease. Many studies target PTB domain-containing proteins in order to inhibit binding to  $\beta$ -APP preventing amyloid formation; whereas others target inhibition of specific aspartate proteases required for amyloid plaque formation. The role of GSK-3 is actively being studied in addition to specific inhibitors to this target for AD. Structural examples analyzed include Presenilin Homologue (PSH) protein and Mint1 which are important for the regulation of  $\beta$ -APP.

Recent studies are reviewed, examining inhibition of the aspartic protease BACE\_1, which is known to cleave  $\beta$ -APP to  $\beta$ -amyloid, essential to the formation of  $\beta$ -amyloid plaques. A structural analysis of BACE\_1/inhibitor complexes is provided with suggested modifications to increase bioavailability of inhibitors. Novel techniques utilizing nanoparticles to destroy  $\beta$ -amyloid plaques is introduced as a possible future therapy for AD. Preliminary characterization and analysis of nanoparticle sizes to deliver GSK-3 inhibitors is presented.  $\beta$ -APP presents a formidable challenge as a target for drug development to

block  $\beta$ -amyloid [plaque](#) formation ( $\beta$ -APP cleavage) in AD. A more direct approach to combat AD is the inhibition of the aspartic protease BACE\_1. The role of GSK-3 in AD introduces a new level of complexity in the pathophysiology of AD. The current focus of many studies is to employ methods of drug delivery to these known targets via nanoparticles and microspheres.

**More information:** Harolin M. Sosa et al. Structural Analysis of Relevant Drug Targets for Alzheimer's Disease: Novel Approaches to Drug Development, *Current Bioactive Compounds* (2017). [DOI: 10.2174/1573407212666160607091117](#)

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