Scope of Amyloid Formation Inhibitor Development Targeting β-Secretase

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive dementia accompanied by extensive neuritic plaque in brain caused by deposition of amyloid fibrils consisting of amyloid ß peptides (Aß). Two kinds of proteases cleave the one transmembrane precursor protein (APP) consisting of about 700 amino acid residues, and produce Aß. Aß is located in the extracellular and transmembrane region in APP. ß-Secretase cleaves the N-terminal part of Aß, and then γ-secretase cleaves C-terminal part. The typical isoforms of Aß are Aß40 with C-terminal Val and Aß42 with 2 amino acids (Ile-Ala) extended at C-terminal. Aß42 shows higher aggregating tendency than Aß40. Since the aggregated Aß42 entangles Aß40 and forms amyloid fibrils, accumulation of Aß42 is considered to be deeply involved in onset of AD. α-Secretase cleaves APP at the different site from ß-secretase and inhibits the production of Aß.

In 1999, the structure of BACE1 (ß-APP cleaving enzyme) was determined by cloning and shown to be a transmembrane glycoprotein and an aspartic protease, which drastically accelerated the inhibitor studies. The Aß hypothesis that the accumulation of Aß triggers the onset of AD may be established if drugs to inhibit the production of Aß are developed for therapeutics of AD. At present, BACE1 inhibitors are designed based on substrate transition-state concept and demonstrated that they inhibit Aß production in vivo.