S22-2 Modulation of beta- and gamma-secretases for the treatment of Alzheimer disease

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Genetic and biochemical studies provide strong evidence that the production and the deposition of amyloid-β peptides (Aβ) contribute to the etiology of Alzheimer's disease (AD). Thus, β- and γ-secretases, that are responsible proteases for the Aβ generation, are plausible molecular targets for AD treatment. Both β- and γ-secretases are aspartic proteases that cleave at the N- and C-terminal, respectively, scissile bonds of Aβ. Drugs that regulate the production of Aβ by inhibiting or modulating these secretase activities could provide a disease-modifying effect on AD, although recent studies suggest that both secretases play important roles in several cellular signaling pathways. Thus, understanding the molecular mechanism whereby β- and γ-secretases recognize and cleave the substrates is a critical issue for the development of compounds that specifically regulate Aβ-generating secretase activity. I will review our biochemical, chemical biological and structural studies on the β- and γ-secretases, and envision the direction for developing effective and selective secretase inhibitors as therapeutics for AD.