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Challenges to the enigma of $\gamma$-secretase and to Alzheimer’s disease

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Our interest in Alzheimer’s disease (AD) and in $\gamma$-secretase, a mysterious and fascinating machinery for the production of amyloid $\beta$ peptides (A$\beta$), was aroused by the in vitro demonstration that A$\beta$ ending at position 42 (A$\beta$42) forms amyloid fibrils much faster than A$\beta$40 (Jarrett et al. 1993), the latter being the predominant A$\beta$ species produced by cells. Owing much to the groundbreaking invention by Drs. Nobu Suzuki and Asano Asami of the monoclonal antibodies that discriminate the C-terminal clip-site structures of A$\beta$40 and A$\beta$42 (Suzuki et al. 1994), we were able to visualize these different A$\beta$ species in the brain tissues of patients with AD and Down’s syndrome, showing that A$\beta$42 deposition, typically as diffuse plaques, is one of the earliest changes in the “Alzheimerization” of human brains (Fig. 1; Iwatsubo et al. 1994).

Important discoveries in the genetics of familial AD consolidated the significance of A$\beta$42 in AD: mutations in APP (Suzuki et al. 1994) and presenilin (PS) genes enhance the production of A$\beta$42 by shifting the preferred $\gamma$-secretase cleavage site from position 40 to 42, resulting in an increase in A$\beta$ deposition in brains (Duff et al. 1996: Borchelt et al. 1996). Subsequently, a series of insightful studies, i.e., showing APP metabolism in PS1 KO cells (De Strooper et al. 1998), elucidating the role of the two intramembrane aspartates in PS1 (Wolfe et al. 1999), and photocrosslinking of PS1 fragments with transition-state analogue $\gamma$-secretase inhibitors (Li et al. 2000), unequivocally demonstrated that PS polypeptide comprises the catalytic center of $\gamma$-secretase, which is responsible for the intramembrane proteolysis of APP, Notch and other type I membrane

![Fig. 1. Deposition of A$\beta$42 precedes that of A$\beta$40 in Alzheimerization of human brains. Sections from frontal cortices from patients with Down's syndrome at young [31 y.o. (years old), A and B], middle (44 y.o., C and D) and old (57 y.o., E and F) ages were immunostained for A$\beta$42 (A, C and E) or A$\beta$40 (B, D and F)