Alzheimer’s Disease (AD) is associated with progressive impairments of memory and cognition, genetic causes/risk factors, characteristic neuropathology and biochemistry, and dysfunction/death of specific subsets of neurons in certain brain regions/neural circuits. Disease-defining pathology/biochemistry include the presence of extracellular toxic Aβ42 peptides (oligomers) and intracellular protein aggregates of tau. Over the past several decades, investigators have taken advantage of advances in knowledge of the disease to design therapies for AD. For example, the demonstration of abnormalities of basal forebrain neurons (with cholinergic deficits in the cortex and hippocampus) led to the introduction of cholinesterase inhibitors for symptomatic treatments. Similarly, when information about involvement of glutamatergic systems in ventral-medial temporal lobes in AD was coupled with knowledge of roles of glutamate in excitotoxicity, glutamate antagonists were tried as treatments. Building on several observations by Glenner and by many geneticists regarding Aβ peptides and AD-related genes, investigators have generated a variety of models, particularly transgenic and knockout (KO) mice, that recapitulate some pathologies of AD or alter the expression of proteins critical to pathogenesis. Their models have proved to be of great value in understanding amyloid-related disease mechanisms, in identifying therapeutic targets, and in testing novel treatments. In this presentation, I will comment on these approaches, focusing on the roles of β- and γ-secretase activities in amyloidogenesis and the potential of these enzymes as therapeutic targets for future clinical trials.

In familial AD, mutant genes encoding the amyloid precursor protein (APP) or presenilins (PS1 and 2) influence the levels and/or character of Aβ peptides, which are generated via APP cleavages by the activities of β-secretase 1 (BACE1), and γ-secretase (the PS, Nct, pen2, Aph-1 multi-protein complex). Mice overexpressing mutant APP/PS1 develop age-associated increases in brain levels of Aβ42, Aβ oligomers, neuritic plaques, and deficits in working memory. To gain insights into potential therapeutic targets, Dr. Phil Wong and colleagues targeted genes encoding proteins hypothesized to be critical for pro-amyloidogenic secretase activities. BACE1 −/− mice are viable and do not produce Aβ; moreover, APPswe; PS1 E9; BACE1 −/− mice do not form Aβ deposits or plaques; neither do they show memory deficits. Thus, BACE1, the neuronal β-secretase, is an attractive target for inhibition as part of an anti-amyloidogenic treat-