Abstract: Alzheimer's disease is a progressive neurodegenerative disease that is pathologically characterized by the presence of senile plaques, composed of Ab peptides that are derived from amyloid precursor proteins (APP). Inheritance of mutant genes encoding APP and presenilins (PS) variants cause autosomal dominant, familial Alzheimer's disease (FAD). PS is the catalytic subunit of the g-secretase complex that is essential for intramembranous processing of APP, Notch and several type I membrane proteins and I will present studies aimed at elucidating the structure and activity of the g-secretase complex that is composed of PS, PEN-2, Aph1 and nicastrin (NCT). In parallel studies, we have examined transgenic mice in which the FAD-linked *PS1DE9* transgene can be conditionally deleted in a spatial and temporal manner in order to investigate the impact of mutant PS1 on the proliferation and differentiation of adult hippocampal progenitor cells as a function of environmental enrichment (EE) and exercise. Moreover, we have demonstrated that EE and exercise can largely attenuate Ab deposition in transgenic mice expressing mutant APP and PS1 variants and that conditional deletion of the *PS1DE9* transgene in excitatory neurons has a significant in attenuating these phenotypes. Finally, experiments will be presented that assess the role of the microbiome in modulation of amyloid deposition and neuroinflammation in mouse models of Ab amyloidosis.

In summary, I will present an overview of the molecular and cellular mechanisms by which FAD-linked mutant genes encoding mutant APP and PS1 variants cause Alzheimer's disease.