PSEN1 BUT NOT APP MUTATIONS PRESENT IN MOUSE MODELS OF ALZHEIMER'S DISEASE ATTENUATE THE RESPONSE OF CELLS TO GAMMA-SECRETASE MODULATORS REGARDLESS OF POTENCY AND STRUCTURE

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Introduction: Gamma-secretase modulators (GSMs) inhibit the generation of amyloidogenic Abeta42 peptides and are promising agents for treatment or prevention of Alzheimer's disease (AD). Recently, a second generation of GSMs with favorable pharmacological properties has emerged, but preclinical studies to assess their efficacy are lacking. Such studies rely on transgenic mouse models that express APP and PSEN mutations associated with early-onset familial AD (FAD).

Aims: We have shown that certain PSEN1 mutations attenuated the response of cultured cells to GSMs and potentially confound in vivo studies in AD mouse models. However, different combinations of FAD mutations might have synergistic or opposing effects. The aim of this study was to systematically determine the response of APP and PSEN1 mutations present in current AD models.

Results: Using a potent acidic GSM, we found that single or combined APP mutations did not affect the potency of GSMs. In contrast, all PSEN1 mutations that have been used to accelerate pathological changes in AD models strongly attenuated the Abeta42-lowering activity of GSMs with two exceptions (M146L, A246E). Similar results were obtained with non-acidic GSMs indicating that the attenuating effect cannot simply be overcome by increased potency or structural changes. Notably, two non-acidic compounds fully compensated the attenuating effect of the PSEN1-G384A mutation.

Conclusions: Our findings indicate that most AD models with rapid pathology and advanced phenotypes are unsuitable for preclinical GSM studies. However, we also provide evidence that additional compound screens could discover GSMs that are able to break the attenuating effects of PSEN mutations.