

**P003**  $\beta$ -Secretase activity is not required for generation of the intra-cellular C-terminal domain of the APP family of proteins  
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Overwhelming evidence indicates that the amyloid  $\beta$ -protein ( $A\beta$ ) plays a critical role in Alzheimer's disease pathogenesis.  $A\beta$  is derived from the amyloid precursor protein (APP) by enzymes ( $\beta$ - and  $\gamma$ -secretase) that are leading candidates for therapeutic intervention. APP is a member of a conserved protein family that includes the mammalian homologs, amyloid precursor like protein-1 and -2 (APLP1, APLP2).

APLPs are processed in a manner analogous to APP, with all three proteins subject to ectodomain shedding and subsequent cleavage by  $\gamma$ -secretase.

Here we report that inhibition of BACE alters the normal processing of both APLPs, but that neither the genetic ablation nor chemical inhibition of BACE nor the over-expression of BACE significantly altered APP or APLP ICD production. Furthermore, the production of a  $\sim$ 3-4 kDa peptide derived from APLP1, which we refer to as APLP1 peptide (AP-1) is blocked by inhibitors of  $\gamma$ -secretase, but not of BACE. These results suggest that inhibition of BACE is less likely to adversely effect the normal function of the APP family of proteins than would inhibition of  $\gamma$ -secretase.