# A kunitz domain is a potent inhibitor of KLK6-dependent Aβ42 formation, aggregation and toxicity

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It is commonly held that Alzheimer's disease (AD) is mainly associated with the accumulation of intra- and extracellular amyloid beta-42 (Aβ42) aggregates formed as a result of proteolysis of the amyloid precursor protein (APP) either by amyloidogenic secretases or by Kallikrein-related peptidase 6 (KLK6). As a result of alternative splicing, three major isoforms of APP are produced, namely, APP695, APP751 and APP770. The latter two isoforms contain a kunitz domain, known as APPI, in the extracellular region, whereas APP695 lacks this inhibitor, which remains largely unknown. Our strategy to elucidate the role of APPI in AD as well as developing a potent therapeutic includes targeting the formation of Aβ42 by inhibiting both the proteolytic activity of KLK6 and the formation of extra- and intracellular toxic Aβ42 aggregates.

In my talk, I will present three major aspects that have been examined during my studies: (i) the feasibility of APPI to inhibit Aβ42 aggregation, (ii) isolation of the region within APPI interacting with Aβ42, and (iii) the inhibition effect of APPI embedded within APP on the cleavage of the latter by KLK6.