

A17 Memapsin 2, a drug target for Alzheimer's disease

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Memapsin 2 (β -secretase or BACE) is a membrane associated aspartic protease that initiates the cutting of β -amyloid precursor protein leading to the production of β -amyloid peptide ($A\beta$) and the onset of Alzheimer's disease (AD). Memapsin 2 is currently a major target for the design of inhibitor drugs for treating AD. Information on the structure and intracellular functions of memapsin 2 would contribute to the inhibitor design and applications. We have cloned this human memapsin 2 and obtained the recombinant protease. Crystal structures of memapsin 2 complexed with inhibitors OM99-2 ($K_i = 1.6$ nM) and OM00-3 ($K_i = 0.3$ nM) have yielded the 3-D models of all eight side-chain binding sites of the enzyme. We have also determined the complete sub-site specificity of memapsin 2 and its closest homolog, memapsin 1. Based on these results, potent and small size inhibitors have been synthesized and tested. To provide a therapeutic model of memapsin 2, inhibitors have been conjugated to a 'carrier peptide' to facilitate their transport through cell membranes. We have demonstrated such inhibitors significantly reduced the production of $A\beta$ in cultured cells and in transgenic Alzheimer's mice. These observations support the idea that memapsin 2 is an effective clinical drug target for AD.