

**P015** The evolution of  $\beta$  amyloid cleaving enzyme (BACE1): an Alzheimer's Disease drug target

**Christopher Southan and John M Hancock**

*The European Bioinformatics Institute, Cambridge  
CB101SD and MRC Harwell, Oxfordshire, OX110RD*

The generation of neurotoxic peptides in Alzheimer's disease (AD) includes the proteolytic cleavage of amyloid precursor protein (APP) by beta-secretase (BACE1). Because inhibitors of this enzyme are being developed to treat AD there is a need to illuminate the physiological roles of BACE1 and its paralogue BACE2 by examining their evolutionary history. By searching recent genome data we identified single BACE-like sequences in representative Gnathostomes, Cnidarians, Echinoderms and Ascidians. The 35% to 45% sequence identity with mammalian BACE1 and the C-terminal transmembrane domain demonstrate the clear emergence of this ancestral sequence in chordate evolution. Constructing a tree of over 30 BACE-like sequences showed that BACE2 evolved more rapidly after duplication in fish, suggesting BACE1 has maintained its ancestral function(s). In mammals the Ka/Ks ratio for BACE2 is higher than BACE1 but low in exons encompassing the catalytic site. Genomic searching also established that APP and most of the 8 additional reported BACE1 human substrates had detectable homologues in these basal chordates except the Ascidians. Functional genomics experiments on ancestral sequences could reveal undiscovered roles for mammalian BACE1 and BACE2 that could have implications for BACE1 as a drug target for AD.