

**P001** BACE1 and BACE2 isoform expression and  $\beta$ -secretase enzyme kinetics are altered in the Alzheimer's disease temporal cortex John Stockley<sup>1</sup>, Rivka Ravid<sup>2</sup>, Cora O' Neill.<sup>1</sup>

<sup>1</sup>*Department of Biochemistry, BioSciences Institute, University College Cork, Ireland.* <sup>2</sup>*Netherlands Brain Bank, Meibergdreef 33, 1105 AZ, Amsterdam ZO, The Netherlands*

$\beta$ -secretase is the rate limiting enzyme in the production of  $A\beta$ , thus characterisation of the role of  $\beta$ -secretase in Alzheimer's disease (AD) is important in understanding AD pathogenesis.  $\beta$ -secretase activity is associated with the aspartic proteases BACE1 and BACE2, and BACE1 is the primary  $\beta$ -secretase in human brain. In this study BACE1 immunoreactivity was detected at 75, 70, 50 and 45kDa in human control (n=7) and AD (n=9) brains indicative of its maturation through the secretory system. Significantly decreased levels of the 75kDa (34%,  $p<0.02$ ), 70kDa (53%,  $p<0.05$ ) and 45kDa (45%,  $p<0.05$ ) forms, and increased expression of 50kDa form (83%,  $p<0.01$ ) were detected in AD cases compared to controls. BACE2 was detectable as 75, 70 and 50kDa isoforms in all cases, and reductions in the 75kDa (33%,  $p<0.05$ ) form were observed in AD cases.  $\beta$ -secretase demonstrated saturable enzyme kinetics, and was potently inhibited ( $IC_{50}=60nM$ ) by the selective  $\beta$ -secretase inhibitor KTEEISEVN(stat)VAEF in both C and AD cases.  $K_m$  values for  $\beta$ -secretase activity were not significantly different when comparing C and AD groups. However,  $V_{max}$  values were higher in many AD cases compared to controls, but this difference did not attain significance. The above techniques and immunohistochemical approaches are being used, both in brain tissue and in cultured neuronal cells, to examine the potential regulation of the  $\beta$ -secretase activity, BACE1/2 levels and localisation with respect to AD pathogenesis.