

**P013** Rab5c is a component of the BACE complex

**Richard B. Parsons, Camilla G. Olsen,  
Daryl Subramaniam and Brian M. Austen**

*Dept. Basic Medical Sciences, St. Georges, University of  
London*

Evidence suggests that  $\beta$ -secretase (BACE) associates with a number of proteins as part of a physiologically active complex, and that protein isoprenylation plays a role in BACE activity. Using the cell-line bHEK, we investigated the type of isoprenylation involved and whether members of the BACE complex are isoprenylated. Incubating cells with 50 $\mu$ M simvastatin (SIMVA), which inhibits both cholesterol and isoprenoid syntheses, inhibited the dimerisation of BACE into its 140kDa physiologically-active form and resulted in decreased A $\beta$  production. Co-incubation with 50 $\mu$ M SIMVA plus 400 $\mu$ M mevalonic acid (MA), which maintains isoprenoid synthesis whilst reducing cholesterol synthesis, resulted in the dimerisation of BACE back to its 140kDa form. There was also a positive correlation between MA concentration and A $\beta$  production ( $r = 0.9839$ ,  $p = 0.0025$  using Pearson  $r$  linear correlation analysis). The farnesyltransferase inhibitor CVFM had similar effects to statins, suggesting that farnesyl is the isoprenoid responsible. Labelling proteins with [ $^3$ H]-labelled isoprenoid revealed a 53kDa protein which associates with BACE, which incubation with CVFM demonstrated to be farnesylated. Using immunoprecipitation followed by Western blotting, this protein was identified as the vesicular transport protein Rab5c. These data suggest that farnesylated Rab5c is a component of the BACE complex and is required to stabilise the dimeric form of BACE.