

**P009** Rationally Designed Inhibitors of Amyloid Toxicity  
**Nicoleta Kokkoni<sup>1</sup>, Kelvin Stott<sup>2</sup>, Hozefa Amijee<sup>1,2</sup>,  
David I.C. Scopes<sup>2</sup>, J. Mark Treherne<sup>2</sup>  
and Andrew J. Doig<sup>1</sup>**

*<sup>1</sup>Manchester Interdisciplinary Biocentre, The University of Manchester, Manchester M1 7DN; <sup>2</sup>Senexis Limited, Babraham Research Campus, Cambridge CB2 4AT*

$\beta$ -Sheets are prone to aggregate into amyloid fibrils. This process has been linked to the onset of at least 20 diseases, including Alzheimer's, Parkinson's and type II diabetes. Oligomers are the probable major toxic species; hence molecules which can interfere with amyloid aggregation and oligomer formation may act as therapeutic agents. *N*-methylated peptides (meptides) are a general class of peptide aggregation inhibitors that act by binding to one face of the aggregating peptide, but are unable to hydrogen bond on the other face. We have optimised the structure of meptides targeted towards  $\beta$ -amyloid aggregation, which is associated with Alzheimer's disease. The most active compound was more active than all previously reported peptide inhibitors at lowering  $\beta$ -amyloid toxicity, as shown by cell culture and long term potentiation data. Its related non-*N*-methylated analogues were insoluble and toxic. Rather than by inhibiting  $\beta$ -amyloid aggregation, the most active compounds appear to work by inducing oligomer aggregation into non-toxic fibrils. We suggest that peptides homologous to an amyloidogenic sequence that are *N*-methylated at alternate positions are a general solution to the problem of developing inhibitors of amyloid formation.