
Contribution ID : **77** Type : **Oral**

# Structural Studies of Alzheimer's Disease Amyloid Precursor Protein Dimers

*Friday, 21 November 2014 12:05 (20)*

Amyloid precursor protein (APP) is a type-I transmembrane protein with a large ectodomain (sAPP), a single transmembrane domain and a cytoplasmic tail. It is cleaved by beta- and gamma-secretases to generate amyloid-β (Aβ), a neurotoxic peptide implicated in Alzheimer's disease (AD). APP dimerisation is closely linked to Aβ overproduction. It is also implicated in APP signalling as APP is proposed to be membrane receptor. There are four potential dimerisation sites in APP, three of which are located in the sAPP region. However, the mechanism of APP dimerisation remains unclear. Understanding APP dimerisation mechanisms at the molecular level will not only provide insights into how APP signals but also have therapeutic implications. Several factors are found to regulate APP proteolysis in vivo. To test their impact on sAPP dimerisation, we used in vitro techniques including ThermoFluor, analytical ultracentrifugation and multi-angle light scattering. We found certain metals and sugars synergistically drive sAPP dimerisation, which is associated with conformational changes and increased stability. This discovery has led to the successful crystallisation of sAPP in its dimeric forms. The identities of metal ions were confirmed using anomalous difference Fourier maps. Key features underlying sAPP dimer formation are clearly demonstrated in the structure. Together with results from the solution studies, the crystal structure has provided a leap forward in understanding the mechanism of APP dimerisation and its pathogenic and functional implications. The structure will be used to discover inhibitors of APP dimerisation and Aβ overproduction as possible AD therapeutics.

## Keywords or phrases (comma separated)

Alzheimer's, APP, dimerisation, metal binding, crystal structure

## Summary

**Primary author(s) :** Ms GAO, Chen (Structural Biology Laboratory and ACRF Rational Drug Discovery Centre, St Vincent's Institute of Medical Research, University of Melbourne, Melbourne, Vic, Australia)

**Co-author(s) :** Dr ASCHER, David (Structural Biology Laboratory and ACRF Rational Drug Discovery Centre, St Vincent's Institute of Medical Research, Melbourne, VIC, Australia); Ms CRESPI, Gabriella (Structural Biology Laboratory and ACRF Rational Drug Discovery Centre, St Vincent's Institute of Medical Research, Melbourne, VIC, Australia); Dr MILES, Luke (Structural Biology Laboratory and ACRF Rational Drug Discovery Centre, St Vincent's Institute of Medical Research, University of Melbourne, Melbourne, VIC, Australia); Prof. PARKER, Michael (Structural Biology Laboratory and ACRF Rational Drug Discovery Centre, St Vincent's Institute of Medical Research, University of Melbourne, Melbourne, VIC, Australia); Dr GRIFFIN, Mike (Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Melbourne, VIC, Australia)

**Presenter(s) :** Ms GAO, Chen (Structural Biology Laboratory and ACRF Rational Drug Discovery Centre, St Vincent's Institute of Medical Research, University of Melbourne, Melbourne, Vic, Australia)

**Session Classification :** Structural Biology II

**Track Classification :** Structural Biology