**Unlocking the Mysteries of Alzheimer’s Disease with Macrocyclic β-Sheet Peptides**

James Nowick, Ph.D.

Distinguished Professor, Department of Chemistry

University of California, Irvine

Oligomers of the β-amyloid peptide Aβ have emerged as key species involved in neurodegeneration in Alzheimer’s disease. The 40–42 amino acid peptide aggregates in the brain to form fibrils and toxic oligomers. While the fibrils and the resulting plaques are the visible hallmark of the disease, the soluble oligomers are now thought to be the damaging species responsible for neurodegeneration. Although the structures of the fibrils are becoming relatively well understood, little is known about the structures of the oligomers. By constraining peptides derived from Aβ to a β-hairpin conformation and preventing fibril formation by *N*-methylation, we have discovered that triangular trimers constitute a fundamental building block of amyloid oligomers. Through X-ray crystallography, we have elucidated high-resolution structures of the trimers, as well as the hexamers, dodecamers, and annular pores that the trimers form. We are now beginning to correlate the biophysical and biological properties these oligomers with those formed by full-length Aβ. We have also generated antibodies against these assemblies and identified features that react with these antibodies in the brains from transgenic mouse models for Alzheimer’s disease and individuals who have lived with Alzheimer’s disease. Through these studies, we are gaining new insights into the structures and roles of Aβ oligomers in Alzheimer’s disease.