Alzheimer’s disease (AD) is the most common cause of dementia and is characterized by the presence of misfolded protein depositions or plaques in the brain. Current evidence suggests that soluble non-fibrillar Amyloid-β (Aβ) oligomers are the major drivers of Aβ-mediated neuronal dysfunction and a significant source of the neurotoxicity is mediated by the interaction of Aβ with transition metals (Cu, Fe and Zn) which leads to altered neuronal metal homeostasis, oxidative injury and accumulation of toxic Aβ oligomers. Determining the structure of Aβ oligomers and the details of the Aβ metal binding site are vital steps towards understanding why neurotoxic aggregates and plaques occur – knowledge that is important in the development of new treatments.

Here, we describe the first atomic resolution x-ray crystallographic structure of an oligomeric Aβ(17-42) [p3] fragment [1] constrained within the CDR3 loop region of a shark IgNAR single variable domain antibody [2]. This discovery shows that the structure of oligomers is not like a piece of a fibril. The predominant oligomeric species is a tightly-associated Aβ dimer, with paired dimers forming a tetramer in the crystalline form. The general features of this oligomer match some recent predictions, thus potentially providing a model system for non-fibrillar oligomer formation in AD.

Interfering with metal binding to Aβ is another emerging target for the development of AD therapeutics [3]. We have analyzed in vitro the structure of Aβ(1-16) (metal-binding region) complexed with transition metals [4] and Pt-based inhibitors by combined X-ray crystallography, absorption spectroscopy (EXAFS, XANES) and ab initio density functional calculations (DFT) [4,5].

Keywords: Alzheimer’s, Amyloid-β oligomer, Structure