Cryo-electron Microscopy Imaging of Alzheimer's Amyloid-beta 42 Oligomer Displayed on a Functionally and Structurally Relevant Scaffold

Jinming Wu [1], Thorsten B Blum [1], Daniel P Farrell [2, 3], Frank DiMaio [2, 3], Jan Pieter Abrahams [1, 4], Jinghui Luo [1]

[1] Department of Biology and Chemistry, Paul Scherrer Institute, 5232, Villigen, Switzerland, [2] Department of Biochemistry, University of Washington, Seattle, WA, 98195, USA, [3] Institute for Protein Design, University of Washington, Seattle, WA, 98195, USA, [4] Biozentrum, University of Basel, 4058, Basel, Switzerland.

Email of main speaker: Jinming.wu@psi.ch

Amyloid-β peptide (Aβ) oligomers are pathogenic species of amyloid aggregates in Alzheimer's disease. Like certain protein toxins, Aβ oligomers permeabilize cellular membranes, presumably through a pore formation mechanism. Owing to their structural and stoichiometric heterogeneity, the structure of these pores remains to be characterized. We studied a functional Aβ42-pore equivalent, created by fusing Aβ42 to the oligomerizing, soluble domain of the α-hemolysin (αHL) toxin. Our data reveal Aβ42-αHL oligomers to share major structural, functional, and biological properties with wild-type Aβ42-pores. Single-particle cryo-EM analysis of Aβ42-αHL oligomers (with an overall 3.3 Å resolution) reveals the Aβ42-pore region to be intrinsically flexible. The Aβ42-αHL oligomers will allow many of the features of the wild-type amyloid oligomers to be studied that cannot be otherwise, and may be a highly specific antigen for the development of immuno-base diagnostics and therapies.