Visualization of the core of a modified Amyloid-β polymorph with MicroED

Rebeccah A. Warmack[1,a], David R. Boyer[1,b], Chih-Te Zee[1,c], Logan S. Richards[1,d], Michael R. Sawaya[1,2,3,e], Duilio Cascio[1,2,3,f], Tamir Gonen[2,4,5,6,g], David S. Eisenberg[1,2,3,4,5,h], and Steven G. Clarke[1,2*]

Affiliations:
[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA, USA
[2]Molecular Biology Institute, University of California, Los Angeles, Los Angeles, CA, USA
[3]UCLA-DOE Institute, University of California, Los Angeles, Los Angeles, CA, USA
[4]Howard Hughes Medical Institute, University of California, Los Angeles, Los Angeles, CA, USA
[5]Department of Biological Chemistry, University of California, Los Angeles, Los Angeles, CA, USA.
[6]Department of Physiology, University of California, Los Angeles, Los Angeles, CA, USA

Contact:
[a]rawarmack@ucla.edu, [b]davboyer@g.ucla.edu, [c]chih.te.zee@gmail.com, [d]loganrichards@g.ucla.edu, [e]sawaya@mbi.ucla.edu, [f]cascio@mbi.ucla.edu, [g]tgonen@g.ucla.edu, [h]david@mbi.ucla.edu, *clarke@chem.ucla.edu

Amyloid-β (Aβ) harbors numerous post-translational modifications (PTMs) that may affect Alzheimer's disease (AD) pathogenesis. However, high-resolution structures of amyloid fibrils that contain these modifications remain out of reach, their determination is complicated by difficulty in isolating monomorphic samples in NMR or cryoEM studies. Efforts to characterize the effects of PTMs by crystallography are limited by the recalcitrance of amyloid segments longer than 11 residues to crystallization, particularly those bearing post-translational modification (PTMs)[1]. Here we present the first *ab initio* MicroED structures of a pair of 15 residue segments found in the Aβ fibril core, with and without an Alzheimer's disease-associated isomerization. These 1.1 Å resolution structures share a conserved kinked β-helix-like-turn with complex features similar to those observed previously at lower resolution in the cores of fibrillar Aβ 1-42, as well as a novel pair of protofilament interfaces. Our results suggest that isomerization in this segment facilitates the formation of a more stable form of one novel interface, promoting enhanced fiber formation and stability. The length of these peptide segments, four residues longer than any other crystallographically determined amyloid structures, is key in facilitating its complex fold - a conformation more representative of the full-length Aβ fibrils. Importantly, we have shown that the Aβ core is stable enough to be crystallized and to showcase complex features beyond the steric zipper interface.

References

[1] Colletier, J. *et al.* (2011). *Proc. Natl. Acad. Sci. USA*, **108**, 16938-16943.