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Host: Prof. Rebecca Carrier

Molecular Understanding of Amyloid Structures, Toxicity, and Inhibition

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342 CSC

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Given the continuing rise of human life expectancy and the lack of both preventive and curative therapeutic approaches to combat neurodegenerative diseases, it is imperative to continue the systematic advancement of molecular understanding of these diseases. The misfolding and aggregation of amyloid peptides are believed to associate with the pathological process of many neurodegenerative diseases including Alzheimer's, Parkinson's, and diabetes type II diseases.

Accumulating evidence suggests the "toxic oligomer hypothesis" that small soluble amyloid oligomers are major toxic species responsible for neuron dysfunction and death. Despite the biological importance, atomic resolution structures of amyloid oligomers have not been determined experimentally, which leads to unsolved questions how these oligomers induce their toxic function to neuron cells and how to prevent the formation of these toxic oligomers.

Here, we have developed an integrated platform, combining theoretical models, molecular simulations, and biophysical experiments, to (i) determine a series of atomic structures of $A\beta$, tau, and hIAPP oligomers; (ii) identify membrane disruption mechanisms of ion-leaking channels and membrane thinning by amyloid oligomers; (iii) examine the membrane component effects on interactions of amyloid peptides with lipid membranes; (iv) reveal a potential link between different amyloid diseases via the cross sequence interactions between different amyloid peptides; (v) develop

different types of inhibitors against amyloid aggregation and toxicity. Our findings provide not only a fundamental understanding of amyloid structure, aggregation, and inhibition mechanism at atomic level, but also a practical design of structural-based inhibitors to block pathways to form toxic oligomers and/or to induce membrane disruption, which are critical for the future development of therapeutic agents against Alzheimer's and diabetes II disease.

Jie Zheng is currently Associate Professor of Department of Chemical and Biomolecular Engineering at the University of Akron. He received his B.S. degree in Chemical Engineering from Zhejiang University, China in 1995 and Ph.D. degree in Chemical Engineering from University of Washington in 2005. He was a research scientist working at Prof. Ruth Nussinov lab at NCI, NIH, before joining the faculty at U. Akron in 2007. In 2012, he was early tenured and promoted to Associate Professor. Zheng is the recipient of the National Science Foundation Career Award, 3M Non-Tenure Faculty Award, and Overseas Outstanding Chinese Young Scientist Award. His main research interest focuses on design of better bio-inspired, bio-functional, and biomimetic soft materials for engineering and biomedical applications.