Title:
From Myddosome Assembly in TLR/IL-1R Signaling to the Discovery of Bidirectional FADD-Procaspase-8-cFLIP Assemblies in TNFR1/CD95 Signaling

Abstract:
In innate immunity, IRAK1/2, IRAK4, and MyD88 assemble into myddosome signaling complexes via death domain interactions upon TLR/IL-1R activation. Similarly, FADD, procaspase-8, and cFLIP utilize death effector domains to form signaling complexes in response to TNFR1/CD95 activation. However, unlike the myddosome complex, which primarily activates NF-κB, the assembly of FADD, procaspase-8, and cFLIP determines whether a cell undergoes or resists apoptosis and/or necroptosis. Understanding the mechanisms underlying these processes requires structural insights, as conventional cell biology approaches are insufficient to elucidate the assembly principles of these multiprotein oligomeric complexes.

This lecture will highlight the critical role of three-dimensional structural details in deciphering the complex regulatory functions of FADD, caspase-8, and cFLIP in TNFR1/CD95 signaling. Cryo-EM analysis has revealed multiple FADD-caspase-8-cFLIP assemblies with distinct stoichiometries, leading to the discovery of a unique bidirectional assembly mechanism. These findings provide mechanistic explanations for several key questions: (1) How does cFLIP inhibit apoptotic signaling mediated by FADD and procaspase-8? (2) Why does cFLIP-L, but not cFLIP-S, trigger partial activation of procaspase-8? (3) How does full caspase-8 activation occur in the absence of cFLIP? (4) Why do many tumor cells maintain high levels of cFLIP?

Additionally, cryo-EM structures reveal limitations in AlphaFold predictions, emphasizing the necessity of experimentally resolving the three-dimensional organization of death-domain-fold assemblies. The cryo-EM results and the insights are crucial for advancing our understanding of complicated signaling mechanisms in innate immunity, development, inflammatory diseases, and cancer progression. These insights are also crucial for therapeutic development, offering potential strategies for treating cancers and inflammatory diseases.