Seminar

Dr. Peter Shen

Assistant Professor

Department of Biochemistry, University of Utah

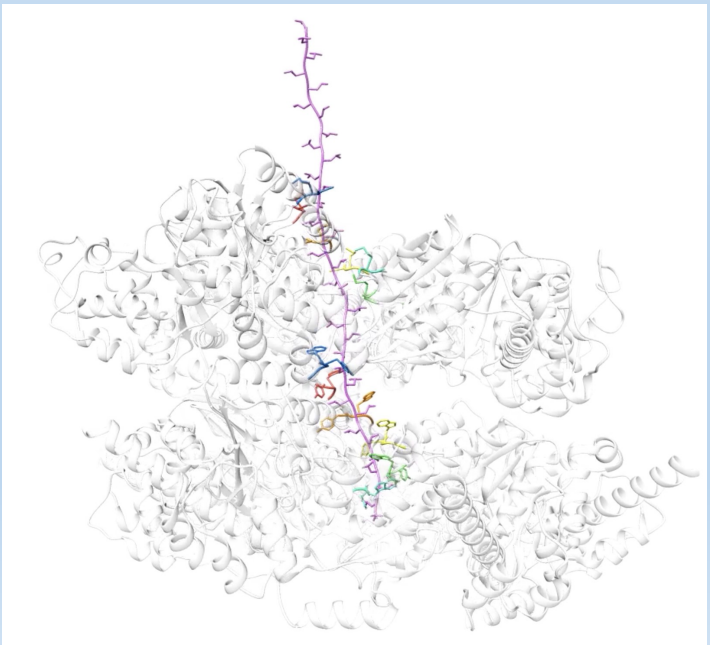
April 24, 2019 at 4:00 pm

In Widtsoe 330

Host: Sean Johnson

Visualizing the mechanisms of protein quality control

Abstract: Optimal cellular function requires a delicate balance between protein synthesis, folding, unfolding, and degradation. The Cdc48 ATPase is a ubiquitous cellular machine that functions in multiple biological pathways by segregating its protein substrates from a variety of stable environments such as organelles or multi-subunit complexes. Missense mutations in human Cdc48 cause a progressive, multisystem degenerative disease, and Cdc48 has also emerged as a target of anti-cancer therapeutics. Cdc48 belongs to the broad family of AAA+ ATPases, but the mechanism of Cdc48 has remained obscure. Its reported structures are inconsistent with models of substrate translocation proposed for other AAA+ ATPases, and information about Cdc48 and other AAA+ ATPase interactions with authentic substrates is limited. We used electron cryo-microscopy (cryo-EM) to determine a 3.7 Å resolution structure of Cdc48 in complex with an adaptor protein and a native substrate. The structure shows how Cdc48 recognizes the adaptor through its N domains and how it engages substrate with both of its ATPase rings. These findings indicate a unified hand-over-hand mechanism of protein translocation by AAA+ ATPases and provide a structural framework to studying Cdc48 in the context of human disease.



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