Investigating the mechanisms of molecular motors using Cryo-EM

By Gabriel C. Lander

Associate Professor, The Scripps Research Institute, USA

Cryo-electron microscopy (cryo-EM) proves to be an increasingly powerful tool for studying macromolecular structures with near-atomic precision, and we use this technique to study AAA+ ATPase motors involved in a variety of cellular processes. One such motor is YME1, an inner mitochondrial membrane AAA+ quality control protease, which forms a closed spiral staircase encircling an unfolded substrate, directing it toward the flat, symmetric protease ring. Our structural work shows how a tightly coordinated network of conserved residues defines a sequential, around-the-ring ATP hydrolysis cycle that results in step-wise substrate translocation. Importantly, these results define a translocation mechanism likely conserved for other AAA+ ATPases.

While high-resolution structures generally depict cellular machinery in a single conformational state, cryo-EM can also be used to explore the conformational landscape of very large, structurally heterogeneous macromolecular systems. We use a combination of 2D and 3D electron microscopy analyses to investigate the dynein motor complex, which plays a critical role in delivering components to specific locations within a cell. We have produced hundreds of 3D snapshots of the microtubule-bound dynein complex bound to a processivity cofactor, dynactin, to gain a mechanistic understanding of this motor’s minus-end directed motion. Our analyses show how multiple dyneins are grouped onto a single molecular scaffold to promote collective force production, increased processivity, and favor unidirectional movement.

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About the speaker
Gabe Lander has been solving the structures of macromolecular machines by cryo-electron microscopy (cryoEM) for over 12 years, using 3D structures to shed light on how protein assemblies interact with the cellular environment. Gabe received his B.S. in biochemistry from Binghamton University, and performed his graduate studies at The Scripps Research Institute jointly under Bridget Carragher, Clint Potter, and Jack Johnson. Gabe then performed his postdoctoral research at UC Berkeley, applying his streamlined cryoEM methodologies to investigate the properties of microtubule dynamics and the mechanism of protein degradation by the 26S proteasome. As an Associate Professor at Scripps Research, Gabe’s group uses cutting-edge cryoEM methodologies and innovative processing algorithms to determine the molecular bases for heart diseases, neurodevelopmental and neurodegenerative diseases, and cancers. Gabe is a recipient of an Innovator Award from the National Institutes of Health, the Amgen Young Investigator Award, and is a Searle and Pew Scholar.