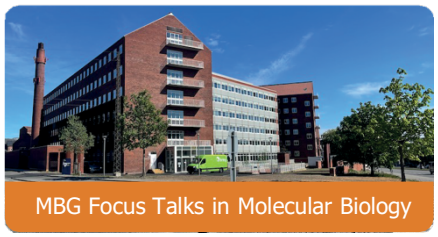
MBG FOCUS TALK

Hosted by Thomas Boesen and Poul Nissen, Aarhus University



Monday 17th February 2025 from 11:00-11:30
In faculty club meeting room (1870-816)

Julia Mahamid

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Enabling discovery by in-cell structural biology

Structural biology has traditionally focused on the structure and function of individual macromolecular complexes, but falls short of revealing how they come together to give rise to dynamic cellular functions. Here, cryo-electron tomography (cryo-ET) provides a unique opportunity for obtaining structural information across a wide range of spatial scales - from small model organisms, intact cells and 3D cultures frozen in their close-to-native state, to the level of individual macromolecules embedded in their native functional environments.

We develop and employ advanced sample preparation techniques for in-cell cryo-ET, including cryo-focused ion beam thinning guided by 3D correlative fluorescence microscopy. Preparations of such site-specific 'electron-transparent windows' enable the assignment of macromolecular structures directly from the high-resolution three-dimensional stills captured by cryo-ET when aided by an array of methods, including computational patter recognition and novel developments of genetically-encoded molecular tags. Using the genome-reduced human pathogen *Mycoplasma pneumoniae* as a minimal cell model, we further demonstrated the synergistic application of whole-cell crosslinking mass spectrometry and cellular cryo-ET to determine an in-cell integrative model of actively transcribing RNA polymerases coupled to a translating ribosomes. Recent computational breakthroughs now allow resolving these molecular machines to near-atomic resolution directly inside the cell, reveal small molecule antibiotics bound to their active site in ribosomes within the intact pathogen, provide snapshots of their structural dynamics along reaction cycles, and illuminate functions of previously unknown macromolecular complexes. Such cutting-edge combinations of methods unlock an enormous potential for both mechanistic studies and system-spanning discovery by in-cell structural biology.

Julia Mahamid is one of the opponents for the PhD defense by Josephine K. Dannersø, taking place 17th Feb. from 13:00 in 1324-011, on "Neuronal functions elucidated by electron microscopy – from calcium transport to the Axon Initial Segment"

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