Project 2

Deciphering Disease Mechanisms Through Cryo-EM of Protein Complexes

Synopsis/Abstract (max 800 words)

Proteins rarely act alone; instead, they function as part of intricate macromolecular complexes that underpin cellular processes. Dysfunction in these protein assemblies often contributes to the onset and progression of diseases ranging from neurodegeneration to cancer. Cryo-electron microscopy (cryo-EM) has revolutionized structural biology by enabling high-resolution visualization of protein complexes in near-native states. This project leverages the transformative power of cryo-EM to investigate the structure and function of disease-associated protein complexes, providing insights into their roles in cellular physiology and pathophysiology.

Our objective is to identify structural determinants that underpin the formation, regulation, and malfunction of protein complexes implicated in various diseases. We aim to explore how these complexes operate under physiological conditions and how mutations or dysregulation drive pathological changes, creating opportunities for targeted therapeutic interventions.

The specific project aims are: i. High-resolution structural determination: Resolve cryo-EM structures of protein complexes linked to diseases such as neurodegeneration, cancer, and metabolic disorders. ii. Impact of mutations: Characterize structural changes induced by disease-associated mutations, correlating these alterations with functional deficits. iii. Dynamic assembly and regulation: Examine how protein complexes are assembled, regulated, and disassembled in response to cellular signals and environmental changes. iv. Molecular mechanisms of pathogenesis: Link structural observations to disease phenotypes, revealing mechanisms such as impaired signaling, altered enzymatic activity, or disrupted protein-protein interactions. v. Integration with complementary methods: Use biochemical assays, molecular dynamics simulations, and cell-based studies to validate cryo-EM findings and establish functional relevance.

vi. Resource development: Create cryo-EM workflows, standardized protocols, and open-access structural databases tailored for disease-relevant protein complexes. This project will enhance the understanding of molecular mechanisms underlying diseases, offering insights into the structure-function relationships of critical protein complexes. By integrating structural data with functional studies, we aim to uncover novel therapeutic targets and advance the development of precision medicines.

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Proposed collaboration within ArchiFun network (not mandatory at this stage):

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Proposed list of secondments (not mandatory, but recommended if known already):

Main ArchiFun theme involved:

Mechanisms of bacterial resistance and cancer onsets;
Neurodegenerative and autoimmune diseases;
Physiology and ecology;

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