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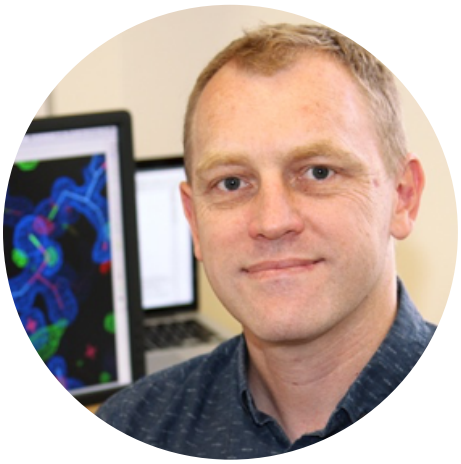
SEMINAR SERIES 2024

9 APRIL

Prof. Brett Collins

Centre for Cell Biology of Chronic Disease,
Institute for Molecular Bioscience,
The University of Queensland

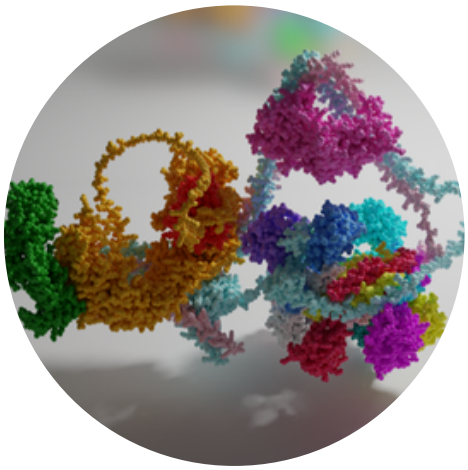


The Collins lab is interested in understanding how molecular interactions between proteins and lipids control intracellular membrane trafficking, using structural biology and biophysical approaches. Current interests include (i) endosomal trafficking by the Retromer complex and the sorting nexin protein family, (ii) the formation of plasma membrane structures called caveolae, and (ii) the mechanisms of synaptic vesicle fusion controlled by SNARE proteins.

After training at Macquarie University (Sydney) with Prof. Bridget Mabbutt and a postdoctoral period at the Cambridge Institute for Medical Research with Prof. David Owen, Prof. Collins returned to Australia in 2006 to take up an NHMRC RD Wright Career Development Award at the University of Queensland, Institute for Molecular Bioscience (IMB). He currently holds an NHMRC Investigator Grant and is Director of the Centre for Cell Biology of Chronic Disease at the IMB, UQ. Career highlights include determining the structure of the heterotetrameric AP2 complex that regulates receptor endocytosis at the plasma membrane (Cell 2002; 2010), providing key insights into the Retromer transport assembly (Nature 2018; Sci. Adv. 2021) and the related Commander complex (eLife 2018; Cell 2023) defining a novel family of sorting nexin proteins that regulate endosomal sorting (Nat. Cell Biol. 2021; Nat. Struct. Mol. Biol. 2016), and providing the molecular insights into the assembly of caveolar membrane coat structures (Dev. Cell 2014; EMBO Rep. 2018; Nat. Comms. 2021).

Structure of the endosomal Commander complex mutated in Ritscher-Schinzel syndrome: combining crystallography, cryoEM and AlphaFold2

The Commander complex is required for endosomal recycling of diverse transmembrane cargos including the amyloid precursor protein linked to Alzheimer's disease and is mutated in the neurodevelopmental Ritscher-Schinzel syndrome. It comprises two subassemblies; Retriever composed of VPS35L, VPS26C and VPS29, and the CCC complex which contains twelve subunits: COMMD1-COMMD10 and the coiled-coil domain-containing (CCDC) proteins CCDC22 and CCDC93. Combining X-ray crystallography, cryoEM and *in silico* predictions, we have assembled a complete structural model of Commander [1]. Retriever is distantly related to the endosomal Retromer complex but has unique features preventing the shared VPS29 subunit from interacting with Retromer-associated factors. The COMMD proteins form a distinctive hetero-decameric ring stabilised by extensive interactions with CCDC22 and CCDC93. These adopt a coiled-coil structure that connects the CCC and Retriever assemblies and recruits a sixteenth subunit, DENND10, to form the complete Commander complex. The structure allows mapping of disease-causing mutations and reveals the molecular features required for the function of this evolutionarily conserved trafficking machinery. Prof. Collins will also discuss some of the technical challenges to solving this structure, compare his work with other cryoEM structures recently published, and describe how AlphaFold2 predictions are providing insights that are now guiding our future studies of Commander structure and function.



[1] Healy MD et al., Cell. 2023, 186(10):2219-2237.e29. doi: 10.1016/j.cell.2023.04.003. PMID: 37172566.