CeMMP Centre for Cryo-electron Microscopy of Membrane Proteins

SEMINAR SERIES 2021

Prof. Patrick M. Sexton

Drug Discovery Biology theme
Monash Institute of Pharmaceutical Sciences
Monash University

Patrick Sexton is a NHMRC Senior Principal Research Fellow and Director of the ARC Centre for Cryo-electron Microscopy of Membrane Proteins. He is a leader in the study of GPCRs, biased agonism, and also on allosteric interactions between GPCRs and other proteins and small molecule ligands. More recently, his team has been at the forefront of the application of cryo-EM to elucidation of the structure and dynamics of GPCRs. Prof. Sexton has published over 300 peer reviewed journal articles and has been cited >24,000 times (Google Scholar).

He is a Clarivate Analytics Highly Cited Researcher (cross-disciplinary), a corresponding member of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification, a member of the Faculty of 1000 (Molecular Pharmacology division) and an elected Fellow of the British Pharmacological Society (BPS). Prof. Sexton's awards include the Australasian Society for Clinical and Experimental Pharmacologists and Toxocologists (ASCEPT) Lecturer award, Endocrine Society of Australia Senior Plenary award, Rand Medal (ASCEPT), Paxinos-Watson Award (Australian Neuroscience Society), Vane Medal (BPS), and the GSK Research Excellence award.

Using cryo-EM to interrogate the structure and dynamics of GPCRs

G protein-coupled receptors (GPCRs) are the largest superfamily of cell surface receptor proteins and a major target class for drug development. GPCRs are inherently flexible proteins that have evolved to allosterically communicate external signals to modulation of cellular function through recruitment and activation of transducer proteins, particularly G proteins. Technological evolution in cryo-EM combined with continuing advances in biochemical approaches for the stabilisation of active-state complexes of GPCRs with different transducer proteins is now enabling structural interrogation of receptor activation and transducer engagement. Moreover, cryo-EM can access conformational ensembles of GPCR complexes that are present during vitrification, which can provide a window into the dynamics of these complexes. Using exemplar receptors, I will discuss how we are using cryo-EM to provide insight into GPCR activation by different agonists, and mechanisms of differential transducer coupling. I will also discuss limitations in static high-resolution structures and how analysis of conformational dynamics of different agonist-GPCR-transducer complexes can contribute to mechanistic understanding of GPCR pharmacology.