CeMMP

Australian Government
Australian Research Council

MONASH University

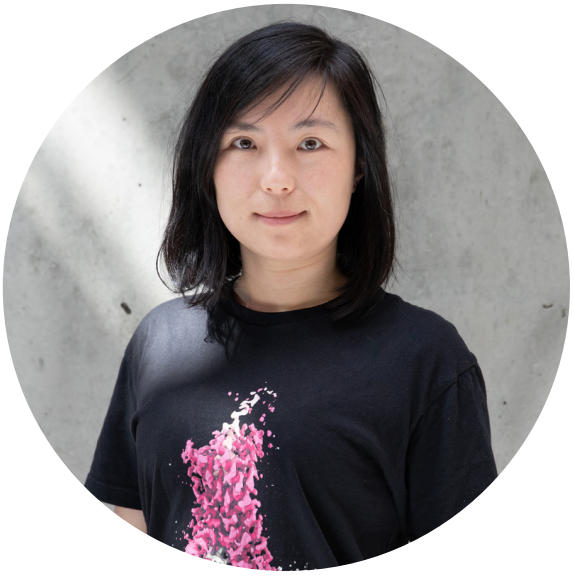
MOLECULAR HORIZONS

WEHI brighter together

SEMINAR SERIES 2024
13 FEBRUARY

Dr Xin (Cindy) Zhang

Drug Discovery Biology
Monash Institute of Pharmaceutical Sciences,
Monash University (Parkville)



Dr Xin (Cindy) Zhang received her PhD in 2021 from Monash University, Australia for structural studies on the glucagon-like peptide-1 receptor in the lab of Profs. Patrick Sexton and Denise Wootten. She was then recruited as a Postdoctoral Fellow to the same laboratory, to work on projects aligned to the Australian Research Council (ARC) Centre for Cryo-EM of Membrane Proteins. Cindy was recently awarded an ARC Discovery Early Career Researcher Award (DECRA) fellowship (2023-2026). Her research program incorporates cell biology, biochemistry, structural biology (in particular cryo-electron microscopy), molecular biology and pharmacology to gain molecular insights into G protein-coupled receptors (GPCRs). Her particular interest is in the structure and dynamics of class B1 GPCRs, to understand how diverse ligands bind to and activate these receptors, which are involved in many physiological processes and are major therapeutic targets for a range of diseases.

Structural insights into the activation and modulation of a class B1 GPCR by small molecule ligands

The glucagon-like peptide 1 receptor (GLP-1R), a class B1 G protein-coupled receptor (GPCR), plays essential roles in regulating insulin secretion, carbohydrate metabolism and appetite, making it a well-established clinical target for the treatment of type II diabetes and obesity. GLP-1R is activated by two endogenous peptides, GLP-1 and oxyntomodulin, and primarily signals through the stimulatory G protein, Gs. While multiple synthetic peptide agonists, such as semaglutide and tirzepatide, have been clinically approved, their use is hampered by side effects and challenges in administration. Hence, there is a growing interest in developing orally available, non-peptidic small-molecule drugs. Several small-molecule drugs have been discovered, but the structural basis of ligand binding and receptor modulation remains elusive. In this study, we determined 11 different cryo-electron microscopy structures of GLP-1R-Gs complexes bound to endogenous peptide agonists, non-peptidic agonists and/or positive allosteric modulators at global resolution of 2.1Å - 3.0Å, which revealed unique ligand binding modes when bound to different ligands. It will also be discussed how these diverse ligands induce distinct complex conformations and receptor conformational dynamics, as uncovered by MD simulation and 3D variance analysis. Together with functional characterization *in vitro*, the observed structural and dynamic differences induced upon binding different ligands provide crucial insights into non-peptide ligand interactions and allosteric modulation. This work sets the foundation for designing novel small-molecule therapeutics for GLP-1R and other class B1 GPCRs.