Structural insights into isoquinoline small molecule ligand-induced agonism and modulation on GLP-1R

Qinghao OU[1,2], *Matthew Belousoff*[1,2], *Fabian Bumbak*[1,2], *Patrick M Sexton*[1,2], *Denise Wootten*[1,2]

[1]ARC Center for Cryo-electron Microscopy of Membrane Proteins, Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, VIC 3052, Australia

[2]Department of Drug Discovery, Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, VIC 3052, Australia

Peptide mono- and multi-target agonists for class B1 G protein-coupled receptors (GPCRs) that co-target the glucagon-like peptide 1 receptor (GLP-1R) with one or more additional receptors are being pursued as novel therapeutics for treatment of metabolic diseases. But developing non-peptide agonists and modulators for these receptors with higher oral availability and lower manufacturing costs remains attractive for next-generation drug discovery. An isoquinoline small molecule ligand termed BI-14185 (one stereoisomer of LSN3451217) was reported to be a agonist and positive allosteric modulator (ago-PAM) at the GLP-1R[1,2]. In the current study, we utilized cryogenic electron microscopy (cryo-EM) to understand the molecular mechanism of agonism and modulation of BI-14185 at the GLP-1R with/without the co-treatment of a peptide agonist. Two potential putative binding pockets for BI-14185 within the GLP-1R TMD were identified, one within the transmembrane helices (TM) core and the second located on the intracellular side of TM 5/6. These two binding pockets shared some similarity to binding sites identified in previously disclosed small molecule ligand-bound GLP-1R structures but they displayed unique interaction patterns with the receptor. The current study advances our understanding about BI-14185-induced agonism and modulation of peptide agonist-mediated GLP-1R responses. With future validation and investigation, this study may benefit design of novel non-peptide agonists/modulators for class B1 GPCRs.

References:

1 Sabnis, R. W. Novel 6-Methoxy-3,4-dihydro-1H-isoquinoline Compounds for Treating Diabetes. *ACS Med Chem Lett* **13**, 891-892, doi:10.1021/acsmedchemlett.2c00220 (2022).

2 Yuliantie, E. *et al.* Isoquinoline small molecule ligands are agonists and probe-dependent allosteric modulators of the glucagon subfamily of GPCRs. *Biochem Pharmacol* **229**, 116483, doi:10.1016/j.bcp.2024.116483 (2024).