Drugging a Hunger Receptor: Structure and Mechanism of Agonist Binding to Novel Vestibular Site in FFAR1

Project ID: 259

Supervisory team

Main supervisor: Prof Imre Berger (University of Bristol)
Second supervisor: Dr Robin Corey (University of Bristol)
Non-academic (CASE) supervisor: Dr Daniel Fitzgerald (Halo Therapeutics)
Other supervisors: Prof Christiane Schaffitzel (University of Bristol)

Collaborators: Dr Chris Tate (MRC Laboratory of Molecular Biology)

Host institution: University of Bristol
CASE partner: Halo Therapeutics

Project description: G protein-coupled receptors (GPCRs) form the largest family of signalling proteins on the surface of human cells, detecting external cues and transmitting them into intracellular responses. With more than 800 members, they control nearly every aspect of physiology and are the target of over 30% of all approved medicines. Despite this enormous importance, many GPCRs remain underexplored because of the technical challenges of studying their structure and function at high resolution.This PhD project will focus on one particularly exciting receptor: the free fatty acid receptor-1 (FFAR1). FFAR1 plays a central role in glucose homeostasis, lipid metabolism and, as recently shown, in regulating appetite via a gut–brain circuit that drives fat preference. This positions FFAR1 as a highly promising target for the treatment of obesity, a global health crisis closely linked to type 2 diabetes, cardiovascular disease, and cancer. FFAR1 is also implicated in idiopathic lung fibrosis and chronic pain, widening the potential scope of therapeutic benefit.Our group has developed novel small molecules that activate FFAR1 by binding to a previously undiscovered extracellular “non-orthosteric” site. Unlike earlier FFAR1 drugs, which were hydrophobic and prone to toxicity, our new oxazole agonists are soluble and chemically distinct from free fatty acid mimics, offering clear advantages for clinical development. These findings open a new chapter in GPCR biology, with broad implications for targeting other receptors in this medically critical family.The goal of this project is to define, at near-atomic detail, how these agonists engage and activate FFAR1. The student will employ cutting-edge cryogenic electron microscopy (cryo-EM) to determine high-resolution structures of FFAR1 in complex with agonists and G proteins, complemented by biomolecular modelling and molecular dynamics simulations to capture the dynamic process of receptor activation. This integrated approach will generate fundamental insights into receptor pharmacology and ligand design.This is an outstanding opportunity for a motivated student to gain expertise at the interface of structural biology, computational biophysics, and pharmacology. The training will combine state-of-the-art experimental methods with

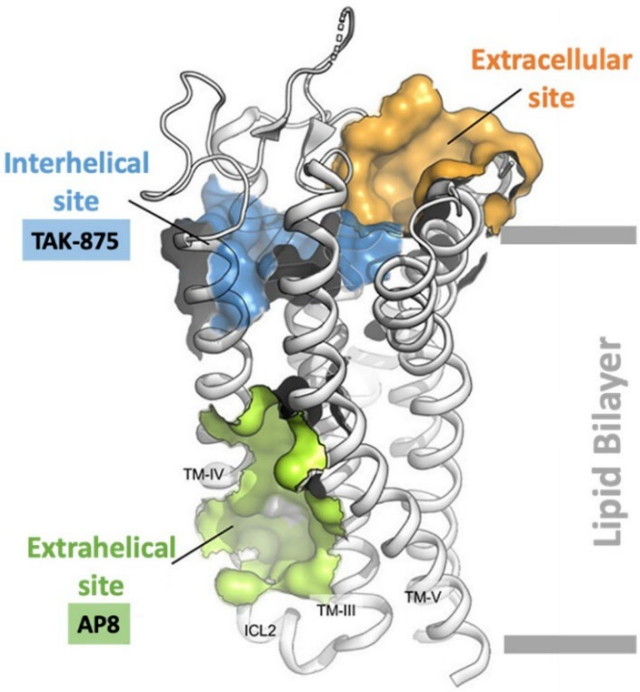


Figure 1: FFAR1 ligand binding sites

advanced computational approaches, while also engaging with drug discovery pipelines and industrial stakeholders.By dissecting a novel mode of GPCR activation, this project promises both high-impact basic science and real translational potential. The findings may ultimately contribute to the development of new classes of medicines for obesity, diabetes, and other major diseases, offering valuable alternatives to current therapies such as GLP-1 agonists (e.g. semaglutide/Wegowy).

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.