Targeted Project / AY 2025 -2026

G protein-coupled receptor signals beyond the cell surface

Project Reference: TRG-PHA-MMS

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BBSRC DTP main strategic theme: Bioscience for an integrated understanding of health

BBSRC DTP secondary strategic theme: Understanding the rules of life

Project outline:

G protein-coupled receptors (GPCRs) are membrane proteins capable of sensing a wide variety of stimuli to control key physiological processes such as neurotransmission, metabolism, and immune responses. Although GPCR signalling primarily stems from the plasma membrane, signalling from specific intracellular compartments is emerging as a novel regulatory layer that could help explain how activation of a single receptor can lead to a diversity of downstream cellular responses. For several GPCRs, this intracellular activation is dependent on the internalisation of their endogenous ligands by organic cation transporters (OCTs). This interdisciplinary project aims to systematically characterise how the subcellular distribution of endogenous GPCR signals determines receptor function. To do so, we will leverage computational systems pharmacology methods to integrate transcriptomics, molecular pharmacology, 3D structure and PheWAS information. By mining publicly available RNAseq datasets across 200 cell types, we will be able to discriminate which cells co-express GPCRs with known intracellular functions together with the OCTs capable of internalising their endogenous ligand, revealing which specific receptor functions can be subject to intracellular activation. By expanding our analyses to the 40 different GPCRs whose ligands are internalised by OCTs, we will identify new candidates to screen for location-specific receptor signalling together with in house and international experimental collaborators. Finally, by combining recently available structural data with genomics information linked to clinical annotations from the UKBiobank, we will explore how OCT missense variants found in the general population can influence endogenous GPCR ligand internalisation, thus altering intracellular receptor signalling and giving rise to specific phenotypic traits and disease predisposition. In this way, this project will boost our understanding of an underexplored mechanism modulating receptor function and illuminate the role of location-specific GPCR signalling in cell (patho)physiology.