Project Details	
Project Code	MRCNMH24Br Corey
Title	How does the membrane environment impact the activity of the μ-opioid receptor?
Research Theme	Neuroscience & Mental Health
Summary	This project will use cutting-edge computational methods to understand how the membrane and cellular localisation impact the activity of the μ-opioid receptor, including how it binds and is activated by different opioid drugs. Along with wet lab functional data gathered with co-supervisors, these findings will generate insights into opioid receptor signalling and pave the way for future therapeutic breakthroughs in both the management of pain and opioid addiction.
Description	The μ-opioid receptor (MOR) is a key player in pain modulation, addiction, and the pharmacological effects of opioid drugs, such as morphine and fentanyl [1]. The membrane plays a crucial role in modulating the activity of many membrane proteins, including G protein-coupled receptors (GPCRs) such as MOR. In particular, membrane features such as curvature and lipid composition, which vary based on membrane type – e.g. presynaptic vs. postsynaptic membranes, are thought to influence receptor function. This location-specific activity is poorly understood but is likely to impact the mechanism of opioid action [2] and contribute to the design of improved opioid drugs. This project will investigate the effect of membrane behaviour and cellular localisation on MOR pharmacology. The project will be interdisciplinary: the primary research will be computational, but the student will be able to learn and implement a variety of wet lab techniques during visits to co-supervisor labs. The main objectives will be to characterise: 1. the influence of membrane lipid composition on MOR: lipid composition varies between membranes. The student will use coarse-grained molecular dynamics (MD) [3] to investigate the interactions of different lipids with MOR, and apply free energy calculations to determine the impact of lipid composition on MOR-opioid binding affinity [4]. 2. the impact of membrane curvature on MOR: membrane curvature can influence the organisation and activity of membrane proteins. The student will use MD to see how membrane curvature affects MOR in terms of dynamics, dimerization, and interaction with opioids and other binding partners. 3. the pharmacology of MOR in lipid raft microdomains: Cholesterol-rich membrane microdomains impact the function of several GPCRs, including MOR. Using state-of-the-art computational methods, such as enhanced sampling, the student will explore how these domains affect aspects of MOR function, including the binding of opioids. This project will employ a range of cutting-edge computational methods, which have emerged as powerful tools in the modelling of biomolecular structures and dynamics, including protein-drug interactions. There will also be opportunity to learn programming and Data Science skills using Python. The computational findings will be validated and given a broader physiological context using functional data generated in the labs of the co-supervisors, all of whom are experts in MOR. This will involve introducing mutations that change the lipid-binding, curvature-seeking, or raft-associating properties of MOR, or genetically/chemically changing

	the membrane lipid composition. Then the student will measure how this impacts MOR activity using: • functional cell-based assays at the receptor level with Eamonn Kelly, including BRET assays to measure G-protein activation, arrestin recruitment, and radioligand binding to MOR [5], • identifying compounds of interest and using analytical chemistry techniques to confirm purity with Steve Husbands [6], • whole-cell patch-clamp electrophysiology in brain slices with Chris Bailey [7], including measuring the impact of identified compounds on MOR activity in different regions of the cell. Aside from the importance of these data in terms of interdisciplinary research, these visits will broaden the student's training by exposing them to a variety of different wet lab approaches. References 1. Sutcliffe KJ, Corey RA et al. (2022) Adv Drug Alc Res; DOI: 10.3389/adar.2022.10280 2. Radoux-Mergault A et al. (2023) Sci Adv; DOI: 10.1126/sciadv.adf6059 3. Souza PCT et al. (2021) Nat Methods; DOI: 10.1038/s41592-021-01098-3 4. Corey RA et al. (2019) J Chem Theory Comput; DOI: 10.1021/acs.jctc.9b00548 5. Ramos-Gonzalez N et al. (2023) Br J Pharmacol; DOI: 10.1111/bph.16084 6. Cueva JP et al. (2015) J Med Chem; DOI: 10.1021/acs.jmedchem.5b00130 7. Lowe JD & Bailey CP (2015) Br J Pharmacol; DOI: 10.1111/bph.12605
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