Project Details	
Project Code	MRCNMH25Br Corey
Title	Unlocking the secrets of fentanyl: exploring the anomalous pharmacology of fentanyl at the μ-opioid receptor
Research Theme	Neuroscience & Mental Health
Summary	Fentanyl is a dangerous synthetic opioid that is responsible for more US overdoses than any other drug, yet much remains to be understood about its pharmacology. This project will explore fentanyl's pharmacology using a range of computational molecular modelling techniques along with wet lab data gathered in the co-supervisors' labs. The research will investigate fentanyl's binding mechanisms at the μ-opioid and other receptors, uncovering the molecular basis for its high overdose risk. The findings will contribute to our understanding of synthetic opioids' impact on public health.
Description	Fentanyl is a potent synthetic opioid that is fuelling an ongoing epidemic of drug overdose deaths in the US. Like other opioids, such as morphine, fentanyl and its derivatives act on the μ-opioid receptor (MOR), which is a key player in pain modulation. However, fentanyl displays an anomalous pharmacology at MOR [1], leading to challenges such as a reduced ability to treat overdoses effectively. Further, unlike classical MOR agonists such as morphine, fentanyl also appears to have pharmacological activity at a range of other receptors, which additionally complicates its treatment. This project will investigate the structural basis of fentanyl pharmacology at MOR and other receptors. There will be a primary focus on computational molecular modelling techniques, however the project will be highly interdisciplinary, combining computational research with Robin Corey (RC) and wet lab techniques during visits to co-supervisors Eamonn Kelly (EK) and Chris Bailey (CB). All three supervisors will be active supervisors on the project. The main objectives will be to characterise: 1. Differences in MOR binding between fentanyl, its derivatives, and classical opioids: with RC, molecular docking and atomistic molecular dynamics (MD, see e.g [2]) will be employed to explore the structural dynamics of fentanyl binding to MOR. The focus will be on identification of secondary binding sites, changes to the orthosteric binding pose, alternative binding pathways [3], and allosteric sites. Data will be tested in vitro with EK, including mutagenesis of MOR followed by BRET assays to measure G-protein activation, arrestin recruitment, and radioligand binding to MOR [4], 2. Interaction of fentanyl and derivatives at non-MOR receptors: preliminary data suggest that fentanyl might act at several non-MOR receptors, partly explaining its high in vivo toxicity. The student will use protein modelling, molecular docking, and atomistic MD in RC's lab to explore this further. Findings will be tested in vitro BRET and radioligand binding assays with EK. 3. Spatiotemporal bias of fentanyl: preliminary data suggest that fentanyl is more potent at presynaptic nerve terminals compared with at postsynaptic sites. The student will use coarse-grained molecular dynamics simulations of large membrane patches to adjust the membrane environment surrounding the MOR to match different cell

	types being studied [5]. This will include lipid composition, and membrane curvature. The findings will be test using brain slice electrophysiology in a range of neurons with CB [6]. This project will utilise cutting-edge computational methods, which have emerged as powerful tools in the modelling of biomolecular structures and dynamics, including protein-drug interactions. There will be opportunities to learn programming and Data Science skills using Python. The computational findings will be validated and contextualised using functional data generated in the labs of the co-supervisors. These visits will broaden the student's training by exposing them to a variety of different state of the art wet lab approaches. References 1. Kelly E et al. (2021) Br J Pharmacol; DOI: 10.1111/bph.15573 2. Maloney F, Kuklewicz J, Corey RA et al. (2022) Nature; DOI: 10.1038/s41586-022-04534-2 3. Sutcliffe KJ, Corey RA et al. (2022) Adv Drug Alcohol Res; DOI: 10.3389/adar.2022.10280 4. Ramos-Gonzalez N et al. (2023) Br J Pharmacol; DOI: 10.1111/bph.16084 5. Tzortini E, Corey RA et al. (2023) J. Chem. Inf. Model. DOI: 10.1021/acs.jcim.2c01181 6. Lowe JD & Bailey CP (2015) Br J Pharmacol; DOI: 10.1111/bph.12605
Supervisory Team	
Lead Supervisor	
Name	Dr Robin Corey
Affiliation	Bristol
College/Faculty	Faculty of Life Sciences
Department/School	School of Physiology, Pharmacology and Neuroscience
Email Address	robin.corey@bristol.ac.uk
Co-Supervisor 1	
Name	Professor Eamonn Kelly
Affiliation	Bristol
College/Faculty	Faculty of Life Sciences
Department/School	School of Physiology, Pharmacology and Neuroscience
Co-Supervisor 2	
Name	Dr Chris Bailey
Affiliation	Bath
College/Faculty	Faculty of Science
Department/School	Department of Life Sciences
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	