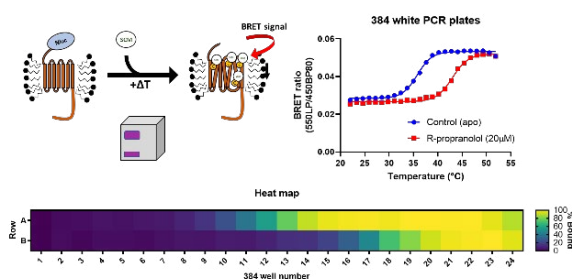


Biophysics without protein purification: Tools to characterise drug action at GPCRs

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GPCRs are large in both number and their portion of approved drug targets. However, studying these proteins biophysically has been made all the more difficult by their membrane environment. Most methods of biophysical study rely on lengthy purification steps of large volumes of protein, separated from their lipid environment and the large number of associated molecules that inhabit this cellular fraction. Drug discovery requires higher throughput tools that work without purification, however, are sensitive to small changes in the GPCR systems. We developed ThermoBRET™ and its associated technology, ModuMelt™, to detect GPCR stabilisation by both orthosteric and allosteric ligands. We can use these technologies to report ligand affinity without the need for protein purification or known ligands. We can take this step further, using identified ligands to assess the effect of allosteric ligands on orthosteric ligand affinity, in a manner that can identify dependency of the allosteric ligand on the orthosteric ligand chosen. Similarly, we have developed SolThermoBRET, a method of applying similar principles to soluble proteins, allowing the detection of ligands and binders. Once complete we can take the study of target receptors and compounds forward into more detail pharmacology, using BRET-based biosensors to more deeply understand the transducers of ligand effects, such as efficacy, ligand and effector binding kinetics, and signalling bias.



Biography

Owen Underwood has a PhD from the University of Nottingham in the molecular signalling and dynamics of the Mu-opioid receptor and has joined the team at Z7 Biotech as a Senior Scientist. He has expertise in assay and technology development with a focus on GPCRs and 8 years molecular pharmacology experience. Z7 Biotech is a precision pharmacology Contract Research Organisation with a speciality in difficult early-stage drug discovery, working with both larger and small pharma and biotech.

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