Chronic effects of G protein-biased mu-opioid receptor agonists in the brain

This project is one of a number that are in competition for funding from the South West Biosciences Doctoral Training Partnership (SWBio DTP) which is a BBSRC-funded PhD training programme in the biosciences, delivered by a consortium comprising the Universities of Bath, Bristol, Cardiff and Exeter, along with the Rothamsted Research Institute. The partnership has a strong track record in advancing knowledge through high quality research and teaching, in collaboration with industry and government.

Studentships are available for entry in September/October 2019.

All SWBio DTP projects will be supervised by an interdisciplinary team of academic staff and follow a structured 4-year PhD model, combining traditional project-focussed studies with a taught first year which includes directed rotation projects.

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Project description

G-protein coupled receptors (GPCRs) are the largest family of targets for approved drugs, with ~35% of current drug treatments targeting GPCRs. However, very few of these are GPCR agonists - drugs that directly activate the receptor. A primary reason for this is that chronic treatment with GPCR agonists can lead to a progressive loss of drug response, known as tolerance. Drug tolerance hinders the development of novel GPCR agonists as future drug treatments, and limits the clinical effectiveness of current GPCR agonists.

The discovery of "biased agonists" at G protein-coupled receptors (GPCRs) has revolutionised the field. Conventional GPCR agonists activate the receptor to cause cellular effect, but then the receptor is desensitized. This desensitization is the predominant mechanism underlying drug tolerance. One advantage of biased agonists is that they can allow GPCRs to signal to cause the desired cellular effect, but the receptors then may evade the usual mechanisms leading to desensitization and tolerance (Smith et al, 2018).

Mu-opioid receptors (MOPrs) are one of the few types of GPCR where agonists are already used in the clinic (eg. morphine for pain relief), as well as being abused on the street (eg. heroin). Tolerance is a significant problem when these drugs are taken long-term. Novel biased agonists at MOPr have recently been discovered, with some entering clinical trials, but, the long term effects of these drugs are yet to be studied.

Although the field of biased GPCR agonists is relatively new, the supervisory team of researchers has many years of experience in studying bias, desensitization and tolerance, particularly at MOPrs (eg. Bailey et al, 2009; Lowe et al, 2015; Hill et al 2016). For the first time, we can now bring together in this application the necessary expertise, experimental approaches and a number of novel biased mu-opioid receptor agonists to study tolerance to biased MOPr agonists.

This project takes a co-ordinated transdisciplinary approach, using a combination of in vivo and ex vivo techniques: behaviour, brain slice electrophysiology, phosphoproteomics. By studying the effects of biased MOPr agonists at a cellular, receptor and whole-animal level we will uncover the mechanisms by which biased agonists induce desensitization and tolerance.

This study is of profound importance for the future of biased agonists as novel and effective drugs, as well as offering a truly translational neuroscience PhD project, using a range of different techniques.

References

Bailey CP et al (2009) Br J Pharmacol 158:157-64

Hill R et al (2016) Neuropharmacology 41:762-73

Lowe JD et al (2015) Mol Pharmacol 88:347-56

Smith JS et al (2018) Nat Rev Drug Discov 17:243-60

Funding

Studentships provide funding for a stipend at the standard UKRI rate (currently £14,777 per annum, 2018/19 rate), research and training costs and UK/EU tuition fees for 4 years.

UK and EU applicants who have been residing in the UK since September 2016 will be eligible for a full award; a limited number of studentships may be available to EU applicants who do not meet the residency requirement. Applicants who are classed as Overseas for tuition fee purposes are not eligible for funding.

Applications

Applicants must have obtained, or be about to obtain, a First or Upper Second Class UK Honours degree, or the equivalent qualifications gained outside the UK, in an appropriate area of science or technology.

Applications should be submitted on the University of Bath's online application form for a PhD in Biosciences. Please ensure that you quote the supervisor's name and project title in the 'Your research interests' section. You may apply for more than one project if you wish but you should submit a separate personal statement relevant to each one.

The deadline for the receipt of applications is Monday 3 December 2018.