

Full details of the proposed research project

Role of ligand residence time in intracellular signalling by cannabinoid G protein coupled receptors.

Host

Professor Dmitry Veprintsev, Professor of Molecular and Cellular Pharmacology, School of Life Sciences, Faculty of Medicine and Health Sciences.

Description of the proposed project

G protein coupled receptors (GPCRs) translate binding of hormones into intracellular signalling by G proteins and another class of proteins called arrestins. GPCRs are important pharmacological targets, and over 150 different GPCRs are targeted by ca 500 drugs used in the clinic.

Ligands can induce signalling responses of varying degree, depending on their strength or efficacy.

Our group is focusing on understanding of how drugs act on G protein coupled receptors (GPCRs) at molecular and atomic levels, and how we could use this understanding to design novel drugs. We combine protein engineering, high throughput mutagenesis, biophysics, structural biology, pharmacology, structural bioinformatics and machine learning approaches to tackle this problem. We complement our research by developing novel fluorescence- and bioluminescence based techniques to measure ligand binding kinetics and kinetics of receptor signalling.

Because the activation of G proteins and arrestins takes time, this project will investigate a hypothesis that the ligand residence time may have a significant influence on the signalling, using cannabinoid CB1 and CB2 receptors as an example. The student will measure the ligand residence time for a test of ligands, and correlate the results with the ability of the ligands to induce signalling response, their efficacies using advanced fluorescence kinetic ligand binding methods and BRET-based signalling biosensors.

We will be delighted to host the student in our laboratory for the summer project of 8 weeks should they be granted the studentship.

They will be a part of my group (4 PhD students and 3 postdocs), as well a part of very vibrant Centre of Membrane Proteins and Receptors, a international flagship research institute focusing of GPCR research and vibrant community of over 20 PhD student and postdocs. This will allow the student to expand their academic network and explore the possibilities for the future career.

I can also confirm that we have the funds to cover the research costs for this project.

This project would suit a full time student or a student working on a part-time basis over a longer period.

What overall scientific training will the student receive during the project?

The student will be trained in mammalian cell culture, in vitro labelling of GPCRs with fluorescence labels, TR-FRET based kinetic ligand binding assay and BRET-based G protein activation and arrestin recruitment assays. They will be trained in the data analysis of ligand binding and activity data. In addition they will present their work to fellow students during the group meeting and COMPARE talks – so they will develop not only lab skills but also their presentation skills and interpretation critical thinking.

A personal statement from Dmitry

"I think it is very important for students to be exposed to research culture at the earliest opportunity as this allows them to make informed choices about future career steps (eg, Masters, PhD and beyond). Most students we had (we host two summer students each year) have continued for a PhD, some in my lab and some with my colleagues across the world. I also found very rewarding to see the development of the students in this relatively short period of time, and appreciate their contribution to the research direction of the lab."

Is there anyone else who will be involved in the supervision of the student for this project?

Dr Eline Koers, senior postdoctoral fellow, Dr David Sykes, Roche Postdoctoral fellow and PGR students (x4) in various techniques.