OXFORD INTERDISCIPLINARY BIOSCIENCE
Doctoral Training Partnership

Industrial CASE Studentship Advertisement 2022-23

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Project Title:	The Structural and Functional Basis of Defective X-Gating in a Novel TASK-1 Channelopathy Associated with Sleep Apnea

Brief description of project:

This DPhil (PhD) studentship presents an excellent opportunity for world-class graduate training in the area of ion channel structural biology, biophysics, biochemistry, and drug discovery. Overall, membrane protein structure, biophysics and function form a major strategic research theme at the University of Oxford, and so provides an exciting and stimulating environment for research students in these areas.

The student will be involved in a multidisciplinary project aiming to determine the basic structural and molecular mechanisms that control activity of the TASK-1 K2P K^+ channel - we have exciting new evidence that TASK-1 channel gating (i.e. opening/closing) becomes defective in a novel channelopathy linked to sleep apnea. This is a common sleep disorder affecting hundreds of millions of people worldwide and is a major public health burden with a significant economic impact. Consequently, there is an unmet clinical need for more effective treatments, but the underlying molecular mechanisms involved are often unclear.

We have recently shown that these new DDSA mutations cluster near the 'X-gate', a novel structural gating motif we recently identified in a closed-state crystal structure of TASK-1 (Rödström et al, *Nature*, 2020). These mutants all produce a marked gain-of-function in channel activity. Importantly, they also render TASK-1 insensitive to GPCR-mediated inhibition thereby amplifying the gain-of-function effect, and we show these defects arise from dysfunctional X-gating. Fortunately, we also discovered that many TASK-1 inhibitors, including those currently in clinical trials, still inhibit the mutant channels thereby offering possible therapeutic strategies for these patients as well as for those with sleep apnea.

Based on these findings, and a range of new experimental tools we also have available, this project aims to understand the structural and functional basis for these defects in TASK-1 channels and their mechanism of regulation by GPCR coupled pathways in both health and disease. It will also address the molecular mechanism of action of new drugs currently being developed to target these channels.

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The project will provide an opportunity to learn a range of experimental techniques (membrane protein expression and purification, nanobody production, and structural biology techniques including x-ray crystallography and cryo electron microscopy), as well as methods involved in the functional analysis of channel regulation by small molecules (ion channel electrophysiology, membrane biophysics, and pharmacology). It will also allow the successful candidate to gain direct experience of working with a major pharmaceutical company.

The student will be based in the brand new Kavli Institute for Nanoscience Discovery in Oxford, but will also interact closely with the industrial supervisor at Bayer who can provide access to a variety of novel tools, expertise and resources not normally available in a standard academic environment. It is also expected that the student will spend a period of three months on secondment with Bayer during the course of this project. Importantly, the student will also have the opportunity to benefit from the training and networking opportunities available as part of the Interdisciplinary Bioscience DTP.

References:

Rödström KE, *et al* (2020) A Unique Lower X-gate in TASK Channels Traps Inhibitors within the Vestibule. ***Nature*** 582:443-447

Kaplanis, J *et al.* (2020) Evidence for 28 genetic disorders discovered by combining healthcare and research data. ***Nature*** 586, 757-62

Sörmann J *et al* (2021) Defective X-gating caused by *de novo* gain-of-function mutations in *KCNK3* underlies a developmental disorder with sleep apnea (open access pre-print) ***medRxiv*** https://doi.org/10.1101/2021.08.05.21261490

Attributes of suitable applicants:

The student will be expected to have a first class or upper second class degree (or equivalent) in a relevant discipline, and to have a genuine enthusiasm and ability for working in a highly collaborative and multidisciplinary research environment.

How to apply:

Applicants should first contact the lead supervisor to discuss whether their research interests are a suitable fit for the project, then apply online via this webpage Interdisciplinary Bioscience (BBSRC Doctoral Training Partnership) | University of Oxford. Please note that we are implementing measures to limit implicit bias in the application process and taking positive action to support students from groups that are under-represented in bioscience. Applicants therefore need to follow the instructions available on the following webpage when preparing an application: Pilot assessment procedure: MPLS doctoral training courses | University of Oxford.

Funding notes:

This project is funded for four years by the Biotechnology and Biological Sciences Research Council UKRI-BBSRC. UKRI-BBSRC eligibility criteria apply (https://www.ukri.org/files/funding/ukri-training-grant-terms-and-conditions-guidance-pdf/). Successful students will receive a stipend of

no less than the standard UKRI stipend rate, currently set at £15,609 per year, which will also be supplemented by the industrial partner

This project is supported through the Oxford Interdisciplinary Bioscience Doctoral Training Partnership (DTP) studentship programme. The student recruited to this project will join a cohort of students enrolled in the DTP's interdisciplinary training programme, and will participate in the training and networking opportunities available through the DTP. For further details, please visit www.biodtp.ox.ac.uk. The DTP and its associated partner organisations aim to create a community that is innovative, inclusive and collaborative, in which everyone feels valued, respected, and supported, and we encourage applications from a diverse range of qualified applicants.