OXFORD INTERDISCIPLINARY BIOSCIENCE
Doctoral Training Partnership

Industrial CASE Studentship Advertisement – 2023 Entry

Supervisor(s) names:	Professor Simon Newstead, Dr Joanne Parker, Dr Ali Jazayeri & Dr Katharina Dürr
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Project Title:	Deciphering the lipid code for lysosomal channels and transporters in inflammatory, metabolic, and neurological disorders.

Brief description of project: The lysosome has emerged as a central signalling centre within the eukaryotic cell. A key role for membrane proteins in the lysosomal membrane has been identified, as signalling systems that recruit kinases to activate downstream signalling pathways. These pathways control metabolism and cell growth, trafficking and autophagy and inflammation. Solute Carrier (SLC) proteins and ion channels have been linked to the activation and regulation of these signalling systems, although the mechanism and molecular details are scarce. In recent years mounting evidence has indicated an important but unclear role for lipids in mediating the function of SLC proteins and linking disease phenotypes to dysregulation of lipid interactions in the cell. Recent work in our group has discovered that phospholipids can regulate oligomeric state, control on/off states and regulate trafficking in the cell. However, a mechanistic understanding and roadmap of lipid regulated functions within the lysosomal SLC family remain elusive.

Our project, in partnership with OMass therapeutics, will directly address this question through a unique combination of in vitro and in vivo biochemistry, structural studies using cryo-EM and native mass spectrometry (MS) coupled with lipidomics. Specifically, the student will use a range of synthetic nanobodies targeted to lysosomal membrane proteins and use these binders to affinity purify the target proteins for subsequent lipid analysis using native MS. These studies will be complemented with in vivo nanodisc reconstitutions, which will enable native-like purification of the proteins for single particle cryo-EM. Insights gained from the native MS data will be used to assign lipid densities in the cryo-EM maps, whilst also serving to inform and direct in vitro transport assays in liposomes of defined lipid composition. The resulting data will be used to develop a blueprint for understanding the importance of specific lipid types (phospholipid vs. cholesterol) in SLC biology, advance our understanding of this neglected aspect of molecular membrane biology and act as a platform for novel drug development.

Further information on the group and recent research can be found on the website www.newsteadgroup.org

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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. Previous research experience in protein biochemistry, structural biology or cell biology is highly beneficial.

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 £17,668 per year.

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.