



Industrial CASE Studentship Advertisement – 2019-20

Supervisor(s) names: *Prof. Liz Carpenter*¹, Prof. Heidi de Wet², plus two industrial supervisors based in Boston, MA.

Department(s)/Organisations:

1. Structural Genomics Consortium, Nuffield Dept. of Medicine, Oxford.
2. DPAG, Oxford.

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Project Title: **Structure and function of key ABC Transporters in health and disease**

Brief description of project (no more than 500 words):

Human ABC transporters are a family of 52 integral membrane proteins that transport diverse molecules across cell membranes. Mutations in ABC transporters cause a range of diseases, including diabetes (ABCC8 and ABCC9), cystic fibrosis (ABCC7, CFTR) and blindness (ABCA4).

At the SGC in Oxford Prof. Liz Carpenter and Heidi de Wet's groups study the 3D structures and function of human ABC transporters, involved in diseases. In particular Liz Carpenter's group works with a range of proteins involved in neuropsychiatric disease, cancer, rare and metabolic disease, as well as inflammatory diseases. Although membrane proteins are thought to be challenging to study, this field is just now opening up with new technical developments, including novel methods for producing proteins, for crystallisation for X-ray crystallography and for obtaining high resolution structures by electron cryo-microscopy.

As human integral membrane proteins are challenging to study at the protein level, the student would start with a range of projects, develop 2 or 3 projects of different levels of difficulty and then select the most interesting and well-behaved proteins to work on. We do have a number of projects where the proteins are already purified, as well as other interesting targets where this aspect of the project would require development.

This project would involve production of a range of human ABC transporters, particularly those associated with disease. The student would then study their structures using cryo-EM with a range of nucleotides, nucleotide analogues, substrates and inhibitors. These structures will provide an atomic level understanding of how these proteins function. They would also use functional assays, including ATPase activity assays, transport assays and biophysical assays to further their understanding of the function of these proteins in health and disease. This work is in collaboration with supervisors at a major pharmaceutical company, who have expertise in producing and studying the structures of complex proteins. They are also experts



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in developing assays to identify small molecule stabilizers and activators for transporters, techniques that would be used by the student.

The student will gain a strong working knowledge of ABC transporter structural and functional studies, including biochemical (ATPase activity, transport assays) and biophysical methods (thermostability, microscale thermophoresis, SPR) and structural techniques, including cryo-EM and X-ray crystallography. The student will spend most of their time working in Prof. Liz Carpenter's group at the SGC, in Oxford, with a team of 14 membrane protein structural biologists. They will also collaborate with Prof. Heidi de Wet, in DPAG, Oxford, for functional studies. This project provides an outstanding opportunity to work extensively with enthusiastic collaborators in industry, including a 3 or 4 months visit to work with your industrial supervisors in Boston, USA.

Attributes of suitable applicants:

The successful candidate will be highly motivated, with a strong drive to work with challenging proteins, learn and develop new methods and understand the fundamental biology of proteins involved in human disease. They will have a good degree in a biological science with a strong interest in understanding and studying protein structure and function, together with a willingness to work both in industrial and academic settings.

Funding notes: This project is funded for four years by the Biotechnology and Biological Sciences Research Council BBSRC. BBSRC eligibility criteria apply (<https://www.ukri.org/files/legacy/publications/rcuk-training-grant-guide-pdf/> Annexe 1). EU nationals who do not meet BBSRC residence criteria are encouraged to contact the programme administrator to check their eligibility for BBSRC funding before submitting a formal application. Successful students will receive a stipend of no less than the standard RCUK stipend rate, currently set at £14,777 per year, which will usually 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 be able to take full advantage of the training and networking opportunities available through the DTP. For further details please visit www.biodtp.ox.ac.uk.