OXFORD INTERDISCIPLINARY BIOSCIENCE
Doctoral Training Partnership

Industrial CASE Studentship Advertisement – 2021-22

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Project Title:	Single particle cryogenic super-resolution microscopy solves multi-protein structures of nuclear pore complexes

Brief description of project:

Protein complexes are single multi-molecular machines delivering a variety of biological functions in cells. It is instrumental to decipher the structures in order to comprehend the mechanisms of life. Nuclear pore complexes (NPCs) are multifaceted and intricate protein complexes essential to all eukaryotic life. They are embedded throughout the nuclear envelopes, providing aqueous protein channels to regulate the transport of many macromolecules. Cryogenic electron microscopy (cryo-EM), a Nobel Prize winning imaging technology (2017), has emerged for determining structures of protein complexes to near-atomic resolution, however the imaging is lacking of protein specificity. Super-resolution single molecule localisation microscopy (SMLM), another Nobel Prize winning imaging technology (2014), takes advantage of protein-targeted fluorescent labelling and gains the distinctive feature of protein specificity, in addition to its nanometre scale resolution.

The marriage of single particle analysis (SPA) in cryo-EM and SMLM gives optical microscopy the power to resolve 3D molecular structures, yet raises some challenges too, e.g. massive data volume. Furthermore, some inherent issues, i.e. chemical fixation artefacts and presence of missing information, in conventional SMLM have to be addressed. We propose to develop cryogenic interferometric SMLM to obtain isotropic 3D super-resolution images of intact protein complexes preserved by flash freezing, and deploy Artificial Intelligence algorithms capable of fast and direct 3D SPA image reconstruction. This exciting new technique will enable robust high-precision protein-specific structural determination in NPC protein complexes. In general, this work represents a substantial leap in the development of light microscopy as a tool for structural biology, and it is widely applicable to many biological systems ranging from protein complexes to small tissue sections, facilitating direct structural observation together with functional elucidation.

The appointed student will carry out the proposed research at the Central Laser Facility OCTOPUS imaging facility. Our labs are built in the Research Complex at Harwell (RCaH) situated at beautiful rural South Oxfordshire. The RCaH is renowned for its world leading multi-disciplinary scientific research across life and physical sciences. The student will become an active member in a small research team embedded in a large national imaging facility, taking advantage of full attention

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from committed supervisors and also abundant resources and assistance around you. The student will receive extensive training on the development and prototyping of advanced optical microscopy, and gain the opportunity to perceive the applications of various optical imaging methods in different biology sciences.

The student will also have access to the world-class biological research facilities at Rosalind Franklin Institute (RFI) in close vicinity to RCaH. RFI is a multi-million-pound new national institute dedicated to transforming life sciences through interdisciplinary research and technology development. The student will receive systematic training in molecular genetics and protein complex sample preparation at RFI.

The student will undertake a 12-week placement at the biopharmaceutical giant AstraZeneca (AZ). Each year AZ invests US-$ 5.9 bn in its science pipeline in order to discover and develop the next generation of life changing medicines. The student will join a team of data scientists, at the Discovery Sciences division at Cambridge, to develop data analysis solutions to high dimensional datasets, providing quantitative insights to biology. The student will also have the opportunities to receive training on Cryo-EM delivered by our in-house structural biologists in AZ, giving critical information for real-world biological study and biopharmaceuticals.

Attributes of suitable applicants:

Applicants require at least an upper-second class degree (or equivalent) in Natural Science disciplines including, but not limited to, Physics, Biology, Chemistry, Biophysics, Biochemistry, Bioengineering or Physiology. A Master's degree or other research experience is beneficial, though applicants will be assessed relative to their career stage.

Practical experience in either optics, imaging, or programming, would be beneficial but training in all required skills will be provided. Applicants wishing to pursue a career in advanced microscopy and biological imaging are highly encouraged to apply.

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 £15,285 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 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.