High Throughput Drug Screening of a Cancer Target using Room Temperature Serial Crystallography – to start October 2019

Christine Desty Scholarship, fully-funded (Home/EU fees £4630 plus stipend of £15,009) for an MSc by Dissertation (MSD) in the School of Biological Sciences, University of Essex

Background
High throughput structure determination of protein-ligand complexes is an essential part of the drug discovery pipeline leading to the development of new medicines. Current state of the art approaches use automated pipelines to produce structures of complexes from crystals cooled to cryogenic temperatures (100K). However, recent studies have indicated that ligand binding sites and poses may be different between 100K and ambient temperature.

Hypothesis - Microcrystals for serial crystallography have been successfully used to describe enzymatic reactions at ambient temperature [1]. However, the possibility to use this novel and powerful technique to solve the structure of protein-ligand complexes has not yet been explored.

The aim is to solve the structure of a novel drug target, the heterogeneous nuclear ribonucleoprotein A1 protein (hnRNPA1), bound to different compounds using microcrystals for serial crystallography (Fig.1). hnRNPA1 holds great promise as a target for the treatment of Small Cell Lung Cancer (SCLC), an aggressive and fast spreading form of lung cancer with unmet clinical needs [2]. In fact, in SCLC activation of hnRNPA1 leads to downregulation of apoptosis and promotion of cell survival, resulting in resistance to chemotherapy. A such, compounds able to alter hnRNPA1 function could represent candidates for future drug development studies.

Work plan
You will work towards meeting the following objectives:

- Recombinant protein production and crystallisation (months 1-3)
- Measurement of serial crystallography (months 3-8)
- Data analysis and structure interpretation (month 8-12)

Feasibility, Training and Resources
The recombinant expression and crystallization of hnRNPA1 is well established in the Prischi lab, with large crystals diffracting to extremely high resolution allowing fine structural details to be resolved (Fig. 1.A-B). The Hough group has extensive experience in the production of microcrystals suitable for serial crystallography and sample delivery and data collection/processing are well established. As such we anticipate few difficulties in obtaining sufficient data for an MSD. Both supervisors have regular access to Diamond Light Source including for serial crystallography experiments and the Hough group has a long standing and productive collaboration with Diamond staff for method development in this area. You will have the opportunity to conduct experiments at Diamond Light Source, Harwell Campus.

1. Horrell, S., et al., Serial crystallography captures enzyme catalysis in copper nitrite reductase at atomic resolution from one crystal. IUCrJ, 2016. 3(Pt 4): p. 271-81.

2. Roy, R., et al., Emerging roles of hnRNPA1 in modulating malignant transformation. Wiley Interdiscip Rev RNA, 2017. 8(6).

Entry requirements and application procedures
Highly motivated applicants with, or expecting, a good degree in the broad area of Life Sciences are encouraged to apply.
Applications should be submitted electronically by **24th April 2019** see here for details https://www.essex.ac.uk/pgapply/enter.aspx

You are encouraged to contact the supervisor before application: mahough@essex.ac.uk and fprischi@essex.ac.ukIf you have any queries with the online application process, please contact ecrix@essex.ac.uk

For general information about the School of Biological Sciences at the University please visit our webpages http://www.essex.ac.uk/bs/.

The University of Essex
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