University of Essex

Biological Sciences at the University of Essex

A FULLY-FUNDED 3 YEAR PHD SCHOLARSHIP IS AVAILABLE FROM OCTOBER 2018

Utilising styrene-maleic acid copolymers (SMA) for structural studies of membrane transporters associated with bacterial antibiotic resistance and copper homeostasis

Background:
Bacteria possess numerous membrane-transporter proteins, which play key physiological roles, as well as contribute to their virulence and pathogenicity. Understanding the atomic structure of these transporters is critical for gaining insight into their mechanisms of action and ultimately for devising novel approaches to counter bacterial diseases.
Historically every *in-vitro* structural study of membrane proteins, including transporters, **required a solubilisation stage using detergents** to extract the protein from the membrane environment.
Such detergent treatment presents the protein with an unnatural environment, often impacting its folding, which for metal ion transporters can influence ion-coordination and subsequent transport.

Recently, **a new technology of one-step membrane protein extraction from intact cells** was developed based on the **styrene-maleic acid copolymers (SMAs)**, which allows in preservation of the native lipid environment of the proteins and has the added benefits of SMA not being a competitive substrate for efflux pump transporters.

Aims:
In this project **the SMA-technology will be employed to study two different groups of bacterial transporters:**

- the **proton-driven multidrug-efflux transporters, involved in antimicrobial resistance** using prototypical RND-transporters (e.g.AcrB);
- **a copper-homeostasis associated transporter recently identified by Worrall group**, which is of currently unknown structure and based on bioinformatics analysis might be representative of a novel family.

Combining a well-studied and already readily produced RND-transporter on one hand, will ensure **sufficient protein is available for methodological developments relevant to the crystallization of SMA-proteins**, while on the other hand potentially answering a major clinically-important question of antibiotic recognition and binding.
The antimicrobial properties of copper are well documented with pathogenic bacteria utilizing complex transporter systems to combat the initial copper burst from the host upon infection. Therefore, the study of the **second group of transporters will provide important fundamental information regarding the structure and function** of a new class of metal transporter and has the potential for high impact due to the novelty associated with them.

Specific Objectives:

- Optimisation of SMA-stabilised RND-transporter AcrB cristallisation to obtain diffraction quality crystals.
- Once successful, SMA-AcrB crystallization would provide a platform for studying its binding to a number of clinically relevant antibiotics.
- Solving the structure of the novel copper-transporter and associated proteins using hybrid crystallography and electron-microscopy approaches.
- Using the SMA-solubilised transporters for *in vitro* functional analysis.

Entry requirements and application procedures
Informal queries may be addressed in the first instance to Dr Vassiliy Bavro v.bavro@essex.ac.uk or Dr Jonathan Worrall jworrall@essex.ac.uk Applications should be submitted electronically by **28th February 2018**. See https://www.essex.ac.uk/pgapply/enter.aspx for details. The intended start date for this 3-year, fully-funded PhD studentship is 4th October 2018. This scholarship will be to the value of £14,553 per annum plus UK/EU tuition fees.

Please note: International students need to have additional funding to cover the difference in tuition fees which is £11,815.00, evidence will be requested that you have these additional funds.

Applicants should write 500 words explaining why they are interested in this project and submit this with their CV.

This scholarship is generously supported by a bequest from the estate of Professor Peter Nicholls (https://www.theguardian.com/theguardian/2014/dec/30/peter-nicholls-obituary**)**

The University of Essex
In the recent Research Excellence Framework 77% of research at the University of Essex research is 'world leading' or 'internationally excellent' (REF 2014).We offer world-class supervision and training opportunities and our research students work at the heart of an internationally-acknowledged and well-connected research community. In the 2013 Postgraduate Research Experience Survey, 84% of respondents said that they were satisfied with the quality of their research degree. At Essex we win awards for our pioneering student support schemes. We are the most recent winners of the prestigious *Times Higher Education* award for Outstanding Support for Students. Essex is a genuine global community. With more than 130 countries represented within our student body, and 40% of our students from overseas, we are one of the most internationally-diverse universities in the UK.