4 Year PhD Studentship available to start September 2020

Department: Respiratory Sciences

Supervisors: Prof Bibek Gooptu bg129@leicester.ac.uk  
Prof Tim Dafforn (University of Birmingham),  
Prof Geerten Vuister gv29@leicester.ac.uk

Eligibility: UK/EU applicants only

Project Title: Structural, kinetic and functional characterisation of ion channel function in the gal-3-fibrosome

Project Description:

General background: Fibrosis is a common ageing-associated process that affects all organs. It occurs following major or persistent injury and ~45% of deaths in the Western world are directly mediated by this process. Fibrosis maintains tissue integrity but not function, so excessive or progressive fibrosis results in organ dysfunction. Subclinical fibrosis may progress to disease in a subset of individuals, and the same tissue insults lead to different severities of fibrosis in different individuals. Recent developments have shown the potential for antifibrotic medications to slow progression of fibrosis in established disease, though none can yet stop or reverse it. These findings indicate the potential for fibrosis to be modulated to preserve healthy ageing.

The Gooptu group have recently shown how intermolecular interactions in a key molecular assembly at the cell surface, denoted the ‘gal-3-fibrosome’, are crucial in both acute injury and pro-fibrotic responses in the lung. Our preliminary data, and published data from other groups, support the relevance of this molecular assembly in fibrosis in other organs. The proteins that constitute the gal-3 fibrosome, their interactions and conformational behaviour therefore represent attractive targets to treat modulate fibrotic pathways to promote healthy ageing rather than disease.

Objectives: In this project we aim to purify and reconstitute under controlled conditions the ion channels of interest and other associated proteins from the gal-3-fibrosome that are critical for these pathways (including the TGF-β receptor). We will then assess their ability to assemble into a profibrotic unit within a membrane, together and in different combinations,
to determine which direct interactions are key. We will aim to solve the structures of the proteins in isolation (where not already known) and in complex within a pro-fibrotic unit.

**Methods:** The core ‘gal-3-fibrosome’ component galectin 3 will be purified at high yield using a recombinant protocol already running in the Gooptu group. Working with the Dafforn group, the student will use styrene maleic acid lipid particle (SMALP) nanodisc technology that allows a molecular ‘cookie cutter’ approach to isolate the other transmembrane proteins of interest. They will then optimise the reconstitution of these components into larger membrane platforms and protein complexes and/or liposomes to study the intermolecular interactions involved. The SMALP approach may also allow direct isolation of complexes of interest from the cell membrane for structural studies. The student will use relevant structural data to define residues within the different proteins whose interactions seem critical for mediating formation of the larger complex and study the functional consequences of mutating them upon pro-fibrotic readouts at the molecular (TGF-β1 pathway signalling), and cellular functional (scratch test in epithelia, fibrotic matrix production in mesenchyma) levels.

**References:**

Relevant recent publications from the Dafforn group include:
A method for detergent-free isolation of membrane proteins in their local lipid environment.

Relevant recent publications from the Vuister group include:

**Funding details:**
4 year fully funded
Stipend at RIUK rates (currently £15,009 for 2018/9)
UK/EU Tuition fees paid directly to the University
Funds for research consumables

**Entry requirements:**
Applicants are required to hold/or expect to obtain a UK Bachelor Degree 2:1 or better in a relevant subject or overseas equivalent.

The University of Leicester [English language](#) requirements apply where applicable.
How to apply:

Please refer to the application link and guidelines at

https://le.ac.uk/study/research-degrees/funded-opportunities/bbsrc-mibtp

Additional information at https://warwick.ac.uk/fac/cross_fac/mibtp/pgstudy/phd_opportunities/

In the funding section of the application please indicate you wish to be considered for MIBTP Studentship

In the proposal section please provide the name of the supervisor and project.

Include a CV and a personal statement explaining your interest in the project and why we should consider you together with all other relevant application documents.

Project / Funding Enquiries: Prof Bibek Gooptu bg129@leicester.ac.uk

Application enquiries to pgradmissions@le.ac.uk

Closing date for applications - Sunday 12th January 2020