PhD studentship (reference number SCI065)

Can microbiome therapy (FMT) be used to treat Primary Bile Acid Malabsorption (BAM)

A three-year full-time National Institute for Biological Standards and Control (NIBSC) PhD studentship award is available to conduct research investigating how microbiome dysbiosis can cause dysregulation in bile acid synthesis leading to primary Bile Acid Malabsorption. The studentship is in collaboration with The University of Warwick (the awarding body) and University Hospitals Coventry and Warwickshire. The anticipated start date is 30 September 2019.

Project description

Primary Bile Acid Malabsorption, also known as Bile Acid Diarrhoea (BAD), is a condition caused by an excess of primary bile acid in the gut and is characterised by severe chronic diarrhoea and bloating. BAD is often misdiagnosed as Irritable Bowel Syndrome with Diarrhoea (IBS-D) due to similar symptoms, however, the SeHCAT test can be used to diagnose BAD and uptake of this test is increasing across the UK. A recent systematic review of IBS-D patients reported an average of ~ 30 % actually had BAD when tested by the SeHCAT test. Recent improvements in our understanding of how bile acid is regulated have led to the proposal that Faecal Microbiota Transplantation (FMT) may be an effective treatment for BAD.

The primary bile acids Cholic Acid (CA) and Chenodeoxycholic Acid (CDCA) are synthesised in the hepatocytes, conjugated with an amino acid, and secreted into the gut to facilitate absorption of lipids. The majority (> 95 %) are reabsorbed from the gut through active transportation via the apical sodium-dependent bile salt transporter (ASBT), with the remaining bile acids transformed by bacterial-mediated deconjugation and dehydroxylation into secondary bile acids, most of which are excreted[5]. The enterohepatic circulation of bile acids is tightly regulated; Fibroblast Growth Factor 19 (FGF19) is the circulating hormone which regulates bile acid synthesis, and functions by inhibiting CYP7A1 an essential enzyme in primary bile acid synthesis. Production of FGF19 is dependent on the nuclear receptor farnesoid X receptor (FXR) which is activated by the binding of bile acids such as Chenodeoxycholic Acid (CDCA). Thus, in high concentrations of CDCA, FXR upregulates transcription of FGF19 which inhibits bile acid synthesis. However, during BAD, studies have demonstrated FGF19 production is inhibited causing an uncontrolled production of primary bile acid resulting in chronic diarrhoea. Although CDCA is the main known activator of FXR, multiple species of bile acids can act as agonists or antagonists to FXR, leading to a complex feedback system which is dependent on the composition of the bile acids in the gut. The bacteria in the gut (gut microbiome) convert primary bile acids into secondary bile acids, thus controlling bile acid composition. Hence, as the primary controller of bile acid composition, the microbiome is also the primary controller of FXR activation and primary bile acid synthesis. It is therefore hypothesised that adverse changes in the gut microbiome cause BAD[3].

The purpose of this study is to elucidate how changes in the microbiome affect primary bile acid regulation and composition, and test whether using FMT to restore the microbiome can work as a therapy for BAD. Students will be trained in a wide range of molecular microbiology, *in vivo,* molecular biology, and bioinformatic techniques.

References:

1 Qin, J. *et al.* A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59-65, doi:10.1038/nature08821 (2010).
2 Human Microbiome Project, C. Structure, function and diversity of the healthy human microbiome. *Nature* **486**, 207-214, doi:10.1038/nature11234 (2012).
3 Sayin, S. I. *et al.* Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metab* **17**, 225-235, doi:10.1016/j.cmet.2013.01.003 (2013).
4 Lynch, S. V. & Pedersen, O. The Human Intestinal Microbiome in Health and Disease. *N Engl J Med* **375**, 2369-2379, doi:10.1056/NEJMra1600266 (2016).
5 de Aguiar Vallim, T. Q., Tarling, E. J. & Edwards, P. A. Pleiotropic roles of bile acids in metabolism. *Cell Metab* **17**, 657-669, doi:10.1016/j.cmet.2013.03.013 (2013).

Key responsibilities:

- To undertake the research projects in line with the project aims
- To communicate effectively, orally and through written media, undertake presentations at scientific meetings and maintain excellent records.
- To interact regularly and effectively with the supervisors and interact appropriately and effectively with other staff.
- To fulfil the requirements of the University PhD programme and to undertake specific training as required by the host institutions.

In addition to meeting all the academic, security and residency requirements, you will have:

- an academic background in the life sciences
- a demonstrated aptitude in a laboratory setting and motivation to undertake research
- a demonstrated ability to work accurately and precisely
- excellent, demonstrated oral and written communication
- a demonstrated interest in the microbiome
- an understanding of molecular microbiology and bioinformatic techniques

The Medicines and Healthcare products Regulatory Agency enhance and improve the health of millions of people every day through the effective regulation of medicines and medical devices, underpinned by science and research. The Agency is made up of c.1300 staff working across two main centres and peripatetically across the UK and abroad. A centre of the Agency, The National Institute for Biological Standards and Control (NIBSC) is a global leader in the characterisation, standardisation and control of biological medicines, and is the World Health Organization Laboratory for Biological Standardisation. NIBSC plays a major role in assuring the quality of biological medicines worldwide through the provision of biological reference materials, by testing products and carrying out research. Our expert scientists also provide advice on a routine basis and in response to emergencies.

Warwick Life Sciences is an international centre of excellence with more than 80% of research rated as 'world leading or internationally excellent' in the REF 2014 assessment.

Research falls into four themes: Biomedical Science, Biotechnology, Environmental Bioscience, and Plant and Crop Science. This research impacts across a broad range of areas, particularly in crop improvement and protection, biosensing and early medical diagnoses, ageing, animal health, earth biosystems, pollution and environmental

genomics. Facilities support multidisciplinary research programmes across Warwick and with other universities, research institutes and industry both nationally and internationally.

The School teaches a range of undergraduate and postgraduate degrees. The School has approximately 130 staff, 800 undergraduates, 100 Taught postgraduates and 250 PhD students.

The project will be supervised by Dr Gregory Amos (NIBSC), Dr Sjoerd Rijpkema (NIBSC), Professor Elizabeth Wellington (University of Warwick) and Professor Ramesh Arasardnam (University Hospitals Coventry and Warwickshire). The student will be based primarily at NIBSC with placements at Warwick throughout the studentship for specialist training.

Requirements for study at the University of Warwick

- Applicants must be predicted or have achieved a first-class or an upper second class undergraduate degree (or equivalent international qualification) as a minimum in Physical Sciences (e.g. Engineering, Physics, Chemistry, Computer Science, Mathematics, Plant Sciences) or Life Sciences (e.g. Biology, Biochemistry).
- 2 satisfactory academic references
- Submit an English Language test certificate (if appropriate) – acceptable tests can be found at: http://www2.warwick.ac.uk/study/postgraduate/apply/english/englishlanguagealternative/
- It is a requirement that overseas students will show that their ability to understand and express themselves in both written and spoken English is sufficiently high for them to derive the full benefit from the PhD. Please note that the requirement for admission is IELTS 6.5 (with no component scores below 6.0) or equivalent. More information can be found at: http://www2.warwick.ac.uk/study/postgraduate/apply/english/

Funding
Tuition fees and consumables are covered and there is a stipend of £18,500 p.a.

Visas and immigration
Applications are open to UK and EU students only, with demonstration of a right to reside in the UK.

To apply
Send (i) your CV including the name and contact details of two academic referees and (ii) a personal statement of no more than 600 words explaining your interest in this project and aspirations for undertaking a PhD to studentship@nibsc.org by 5.00 pm (UK time) on Sunday 15 March 2019.

Please ensure the studentship reference number is included in the subject line of the email and your personal statement.

If you have a disability defined by the Equality Act 2010 (https://www.gov.uk/definition-of-disability-under-equality-act-2010) you may apply under the UK Civil Service Guaranteed Interview Scheme provided that you meet all of the qualifications, skills, requirements and experience defined as essential for the studentship. You must submit the Guaranteed Interview Scheme Declaration form with your application: this can be found at https://www.gov.uk/government/publications/guaranteed-interview-scheme. At interview all applicants will be assessed solely on merit.

Any offer of a studentship is conditional upon successful background screening which includes, but is not limited to, checks on identity, qualifications and right to study in the UK.