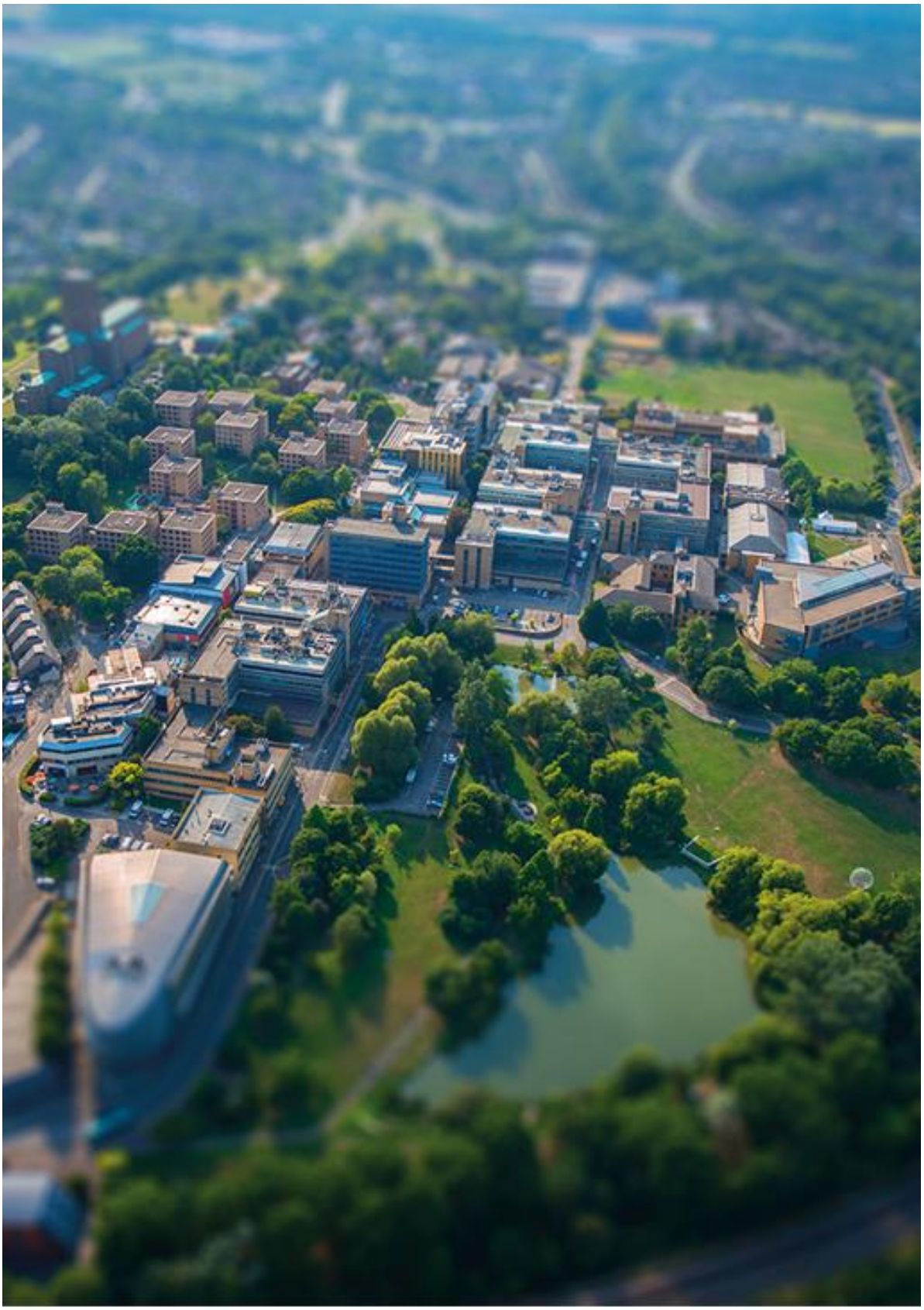
PhD Opportunities for International Scholars in the Faculty of Health and Medical Sciences at the University of Surrey, UK



PhD Opportunities for International Scholars in the Faculty of Health and Medical Sciences at the University of Surrey, UK

Thank you for your interest in studying for a PhD in the Faculty of Health and Medical Sciences. Located in the UK 30 minutes south of London, the University of Surrey provides excellent interdisciplinary research and teaching opportunities in human and animal health.

We are firmly of the belief that excellence in research and teaching in the twenty-first century can only be achieved with an international dimension. We are therefore very keen to invite excellent students across the world to join us in our research projects.

To make an application you will need to identify a supervisor and a project that you are interested in. The following pages provide some of our available PhD projects that are available for students who are seeking to apply for 2019 entry. Further projects, supervisors and email contact details are listed on personal pages under Schools of Study on our website here. You will need to make contact with the supervisor offering this project as you will need their help to complete the application form.

If you wish to apply to study for a PhD in the Faculty of Health and Medical Sciences at Surrey to start in October 2019 you will be eligible to apply for an international fee scholarship.

There are two kinds of fee scholarships available, one reduces your tuition fee to the local UK rate and one provides a 25 % reduction of the International fee. For full information about our fees please click on the link here. https://www.surrey.ac.uk/fees-and-funding/tuition-fees/postgraduate-research-2019-entry

A wide range of exciting research opportunities are described on the Faculty Web pages. We have identified some projects that we would very much like you to consider. These are all presented on our faculty International Page https://www.surrey.ac.uk/fees-and-funding/scholarships-and-bursaries/postgraduate-taught-2018-entry)

If you wish to apply for a PhD place at Surrey you must apply on line for a place before Monday 3rd December 2018. If you also wish to apply for a fee scholarship your application for the fee scholarship must be submitted by Friday 11th January 2019.

Full Information is available on the Doctoral College Web page
https://www.surrey.ac.uk/sites/default/files/2018-10/dcsa3-guidance-notes.pdf

For queries with regards to the studentships please contact: phdstudentships@surrey.ac.uk

For queries regarding your online application please contact: admissions@surrey.ac.uk

Further information:

We have a dedicated International Student Support Team at Surrey who advise on visas and immigration and organises various events for international students. The team understands that leaving your home country to study abroad can be exciting and daunting at the same time. They are able to support you with any questions you may have. Please follow this link to learn more:
https://www.surrey.ac.uk/international

We look forward to receiving your application.

Professor Helen Griffiths, Executive Dean

A selection of topics for PhD study

Table of Contents

A. Cardiovascular

A1 Investigating impact current medication on outcome of peripheral artery disease patients after angioplasty and bypass surgery: focus on platelet inhibitors and oral anticoagulants.

Abstract

Background: Peripheral artery disease due to atherosclerotic stenoses or occlusions of lower limb arteries is increasing worldwide. Revascularization either surgically or by endovascular techniques represent important treatment modalities that are limited by re-stenosis or re-occlusion. Antiplatelet therapy and oral anticoagulation are believed to improve patency of arteries and are typically prescribed over the first 1-3 months after angioplasty or stent placement. However, there are essentially no data supporting this and the bleeding risk is very high in these patients. Therefore, the primary **objective** of this project is to evaluate the efficacy and safety of antiplatelet therapy and oral anticoagulation taken during and after revascularization procedures using routine big data. Secondary objectives are to evaluate the impact of other medications and co-morbidities in this context.

Methodology: Using the RCGP-RSC database linked with the NHS Hospital Episodes Statistics Data, we will first in a repeated cross sectional study evaluate the incidence of lower limb revascularizations including angioplasty, bypass, and endarteriectomy over the last 10 years in the almost 4 Million registered patients and determine the medications patients were on during and after the interventions. In a retrospective cohort study, we will compare the outcome of patients that had received single or dual platelet inhibitors or oral anticoagulants with those not receiving any of these medications during and after interventions. The primary outcomes include major adverse limb events and cardiovascular event and bleeding events in particular in the gastrointestinal tract and brain. Covariates will include other medication and co-morbidities.

References:

McGovern A. et al., BMJ Open 2016; 6:e012801 doi:10.1136/bmjopen-2016-012801;
Correa A. et al., BMJ Open 2016; 20;6(4):e011092; Stegemann E. et al. Angiology 2014 ;
Heiss C. et al. Experimental Gerontology 2018

Training/Skills that will be acquired by the student: Epidemiology, biostatistics, large dataset analysis

Supervisor(s) and brief biography:

Dr Ben Field, graduated in medicine with distinction from St Bartholomew's Hospital, London, in 1997. After specialist training at Guy's and St. Thomas' hospitals, he joined Imperial College London as an MRC clinical research training fellow, obtaining a PhD in 2009 for research into the neuroendocrine control of appetite, energy expenditure and insulin secretion. He is actively involved in research at SaSH and Imperial College, and is an honorary clinical senior lecturer at Imperial College London.

Dr. Martin Whyte, Clinical Senior Lecturer, Dr Whyte trained in medicine at King's College Hospital, qualifying in 1998. During my postgraduate medical training I undertook a PhD at Guy's & St. Thomas' Hospital (University of London) examining the metabolic effects of insulin in critical illness. I then competed my specialist training (CCT) in Diabetes & Endocrinology and General Medicine in 2010. Since 2012 I have combined my NHS Consultant work with that of a Clinical Senior Lecturer at The University of Surrey.

Dr Uy Hoang, is a research fellow working within the Clinical Informatics & Health Outcomes Research Group in the Section of Clinical Medicine Ageing. Alongside specialist medical training in public health at the Oxford Deanery, he also has a doctorate in clinical epidemiology from the Institute of Psychiatry at King's College and a Masters in Public Health from Yale University. His research interests lie around the use of large, routinely collected datasets to study the occurrence and management of chronic physical and mental illness.

Prof Michael Feher, is a Consultant Physician in Diabetes & Clinical Pharmacology and Clinical Lead for lipid, diabetes and hypertension services at Chelsea and Westminster Hospital. He developed and leads unique specialist lipid and diabetes services including lipid clinics in adults and family lipids (joint with paediatrics), new diabetes therapies, liaison-psychiatry-diabetes, and diabetic hypertension

Prof Christian Heiss is a Professor of Cardiovascular Medicine at the University of Surrey and Honorary Consultant the Surrey and Sussex Healthcare NHS Trust. He is an interventional angiologist and cardiologist and has previously headed Vascular Medicine at the University of Duesseldorf, Germany. His research interests include basic mechanisms of vascular homeostasis and human interventions for improvement of cardiovascular health and healthy aging.

Dr Neil Munro is visiting professor of primary care diabetes in the department of clinical and experimental medicine, University of Surrey. He was an associate specialist in diabetes at the Chelsea and Westminster hospital, London from 1998 until 2015 and has worked in specialist hospital based diabetes clinics since 1985. He was also a general practitioner in Surrey from 1984 until 2013 and provided diabetes services to patients of the practice during that time.

Prof Simon de Lusignan, is a senior academic GP and Professor of Primary Care and Clinical Informatics; Chair in Health Care Management; and Head of Department of Department of Clinical and Experimental Medicine at University of Surrey. He is also the Medical Director of the Royal College of General Practitioners Research Surveillance Centre (RCGP-RSC)

Department(s): Department of Clinical and Experimental Medicine

A2 Electrophysiological, molecular and structural characterization of the cardiac autonomic nervous system in ageing – implications for arrhythmia.

Abstract

An ageing myocardium possesses significant electrophysiological alterations that predisposes the elderly patient to arrhythmic risk. Whilst these alterations are intrinsic to the cardiac myocytes, they are modulated by the cardiac autonomic nervous system (ANS) and consequently, ageing of the cardiac ANS is fundamental to the development of arrhythmias. Using a multimodal approach we will aim to clarify the electrophysiological, molecular and structural alterations of the cardiac ANS attributable to ageing. Cardiac stellate ganglia and ventricular ganglinated plexus will be isolated from young and old murine models using established protocols. We will assess for (1) electrophysiological (2) molecular (3) structural properties. Our findings will provide a unique insight into the ageing of the cardiac autonomic nervous system. It is likely that such changes can be attributable to the decrease in functionality and structural alterations to ANS specific receptors in the myocardium with age allowing for targeted intervention that seek to manipulate the ageing ANS.

References: (1) Chadda KR, et al. Ageing, the autonomic nervous system and arrhythmia: From brain to heart. Ageing Res Rev. 2018 Oct 6; 48:40-50. **(2)** Bardsley EN, et al. RNA Sequencing Reveals Novel Transcripts from Sympathetic Stellate Ganglia During Cardiac Sympathetic Hyperactivity. Sci Rep. 2018 Jun 5;8(1):8633. **(3)** Kung GL, et al. Microstructural Infarct Border Zone Remodeling in the Post-infarct Swine Heart Measured by Diffusion Tensor MRI. Front Physiol. 2018 Aug 22; 9:826.

Training/Skills that will be acquired by the student: optical chromatography technique, optical imaging, molecular biology (gene expression, western blot, PCR, immunocytochemistry) and histology.

Supervisor (s) and brief biography:

Dr Kamalan Jeevaratnam (https://www.surrey.ac.uk/people/kamalan-jeevaratnam);
Dr Pradeep Rajendran (University of California Los Angeles);
Prof Kalyanam Shivkumar (http://bioscience.ucla.edu/faculty/kalyanam-shivkumar)

Department: Preclinical Veterinary Sciences, Faculty of Health and Medical Sciences

A3 A novel ex vivo model of heart tissue for drug testing

Abstract
The overwhelming majority of newly designed drugs fail because of side effects on the heart, slowing the development of therapies at great cost to the pharmaceutical industry and the public. A reason for these failures is the absence of simple but representative experimental model systems of adult myocardium that can be utilised for cost effective drug screening and early identification of cardiac side effects.
The aim of this project is to develop and characterise a novel ex vivo model of adult heart tissue for drug testing. Using living porcine hearts readily available from Vet laboratories and abattoirs, we will establish a protocol to prepare viable thin heart slices. Slices viability, structural and functional properties will be characterised using novel imaging and electrophysiological techniques. Clinical drugs will be used to validate the ability of the slices to respond to pharmacological compounds. Furthermore, we will optimise a culture method for the maintenance of heart slices in culture for 2-4 days, enabling the application of heart slices in chronic investigations.
This project will generate a novel ex-vivo multicellular preparation with potential extensive applications in cardiac preclinical research.
References: 1) Wen, …. Camelliti & Lei. J Physiol. 2018 Sep;596(17):3951-3965.
2) Kang, Qiao, Li, Baechle, Camelliti & Efimov. Sci Rep. 2016 Jun 30;6:28798.
3) Camelliti et al., J Mol Cell Cardiol. 2011;51(3):390-8.
Training/Skills that will be acquired by the student: Preparation of heart slices using a high precision vibratome. Functional assessment of heart slices using microelectrode arrays and optical mapping (multicellular electrophysiological techniques). Tissue culture. Cell viability assays. Contractility and force measurements. Molecular biology (RNA extraction + quality control, quantitative real-time PCR, ELISA, western blotting). Immuno-histochemistry and confocal microscopy. Data analysis and statistics. Literature survey and scientific writing.

Supervisor (s) and brief biography: *Dr Patrizia Camelliti, University of Surrey (UK); Professor Igor Efimov, Washington University (US)*
Dr Camelliti is Assistant Professor and Group Leader at the University of Surrey. She holds a DPhil from the University of Oxford. She is a recognised world leader in the field of cardiac biology/medicine, with 31 high-impact publications, 2,960 citations and h-index of 24. Her laboratory is funded by the British Heart Foundation, the Medical Research Council and the Royal Society. Prof Efimov is Chairman of the Department of Biomedical Engineering at George Washington University (US). He is a world-leader in cardiac physiology, with >200 publication and >10,900 citations.

Department: School of Biosciences and Medicine

A4 Development of a 3D ex vivo model of epicardium

Abstract
The recovery capacity of the adult heart after injury is severely limited by the low number of regenerating cells within this tissue. The epicardium, the most external layer of the heart, contains cells able to home to the injured heart muscle and promote its recovery. In this project the student will: (1) develop a model based on pig heart tissues including both the epicardium and underlying heart muscle (2) establish culture conditions for pig epicardial heart slices (3) test treatments to simulate the epicardium and simulate heart disease

Aims:
*Establish an ex vivo multicellular model to observe and quantify epicardial cell behaviour in normal and stimulated conditions
*Validate the model for its ability to replicate the effects of myocardial infarction and treatment previously studied in vivo

Methodology: 3D cardiac tissue culture, electrophysiological assays, tissue transfection, advanced microscopy, 3D imaging, immunofluorescence and confocal microscopy

References:
Smart et al. Nature. 445:177–182. 2006
Katare R,…Campagnolo P,… et al. Circ Res. 2011;109(8): 894-U191
Camelliti P, et al. JMCC 2011;51(3): 390-398

Training/Skills that will be acquired by the student: Primary 3D organotypic cultures, immunofluorescence staining, advanced microscopy, functional in vitro assays, electrophysiology techniques

Skills/qualifications/interests expected of potential student: Critical analysis, writing skills, precision and dedication

Supervisor (s) and brief biography: Dr Paola Campagnolo (http://orcid.org/0000-0002-8957-3969) is Lecturer in Molecular Cardiovascular Biology and coordinates a group composed by one NC3R-funded postdoc, 2 PhD students and 1 MSc student. She is an expert in cardiovascular biology and tissue engineering. Previously, she worked as postdoctoral researcher and successfully supervised PhD students at University of Bristol, Kings College London and Imperial College London
Dr Patrizia Camelliti (https://orcid.org/0000-0002-1346-8089) is Lecturer in Cardiovascular Biology and her BHF-funded research group is interested the characterisation of the cellular and structural remodelling occurring after myocardial infarction. She has developed 3D in vitro models for the study of cardiac cell interaction and function.
The two supervisors have an ongoing collaboration and co-authored an NC3R grant on this topic.

Department(s): Biochemical Sciences

A5 Novel role of pericytes in the vascular complications of dengue disease

Abstract
The aim of this study is to unravel the mechanisms at the basis of the haemorrhagic complications of viral fevers. In particular, this project will study the effect of secreted viral proteins on perivascular cells (pericytes) to assess the consequence on their ability to control capillary permeability and plasma leakage.

Mosquito-borne haemorrhagic fevers are severe diseases that threaten a large population in the developing world. The management of such complications is hampered by the lack of understanding of their biological basis. Haemorrhagic symptoms of dengue are characterised by plasma extravasation and are due to the increased permeability of the capillaries, small blood vessels composed of endothelial and perivascular cells. This study aims at addressing the role of perivascular cells and their interaction with endothelial cells in the context of viral haemorrhagic fevers to uncover new mechanisms that can be therapeutically targeted.

Objectives: 1. Determine the effect of NS1 viral protein on pericytes biology 2. Determine the effect of NS1 viral protein on endothelial cells-pericytes interactions 3. Understand the effect of pericyte NS1 viral protein treatment on vascular permeability

Methodology: Primary vascular cells treated with recombinant viral proteins (commercial or prepared in house) will be tested using a range of in vitro assays and coculture methods (proliferation/viability, migration, 2D coculture, 3D coculture) and analysed by immunofluorescence and microscopy, flow cytometry and fluorimetry.

References:
Campagnolo P, et al. Circulation. 2010 20;121(15):1735-45
Malavige GN, et al. Immunology. 2017 Jul;151(3):261-269
Campagnolo P, et al. Adv Healthc Mater. 2016;5(23):3046-3055.
Sebastian Aguirre,... Kevin Maringer…, et al. PLoS Pathog. 2012;8(10):e1002934

Training/Skills that will be acquired by the student: Human primary cell culture, coculture assays (2D and 3D), advanced microscopy, functional in vitro assays, cloning/protein expression, flow cytometry

Skills/qualifications/interests expected of potential student: Critical analysis, writing skills, precision and dedication

Supervisor (s) and brief biography: Dr Paola Campagnolo (http://orcid.org/0000-0002-8957-3969) is Lecturer in Molecular Cardiovascular Biology and coordinates a group composed by one NC3R-funded postdoc, 2 PhD students and 1 MSc student. She is an expert in cardiovascular and pericyte biology and tissue engineering. Previously, she worked as postdoctoral researcher and successfully supervised PhD students at University of Bristol, Kings College London and Imperial College London

Dr Kevin Maringer (https://orcid.org/0000-0003-0977-8807) is Lecturer in Microbiology and founding member of the University of Surrey Neglected Tropical Diseases Hub. His group is composed of an MRC-funded postdoc and 1 PhD students and 1 MSc student.
The two supervisors have an ongoing collaboration and a shared MSc student working on this topic.

Department(s): Biochemical Sciences and Microbial Sciences

A6 Electrophysiological, molecular and structural characterization of the cardiac autonomic nervous system in ageing – implications for arrhythmia.

Abstract
An ageing myocardium possesses significant electrophysiological alterations that predisposes the elderly patient to arrhythmic risk. Whilst these alterations are intrinsic to the cardiac myocytes, they are modulated by the cardiac autonomic nervous system (ANS) and consequently, ageing of the cardiac ANS is fundamental to the development of arrhythmias. Using a multimodal approach we will aim to clarify the electrophysiological, molecular and structural alterations of the cardiac ANS attributable to ageing. Cardiac stellate ganglia and ventricular ganglinated plexus will be isolated from young and old murine models using established protocols. We will assess for (1) electrophysiological (2) molecular (3) structural properties. Our findings will provide a unique insight into the ageing of the cardiac autonomic nervous system. It is likely that such changes can be attributable to the decrease in functionality and structural alterations to ANS specific receptors in the myocardium with age allowing for targeted intervention that seek to manipulate the ageing ANS.
References: (1) Chadda KR, et al. Ageing, the autonomic nervous system and arrhythmia: From brain to heart. Ageing Res Rev. 2018 Oct 6; 48:40-50. **(2)** Bardsley EN, et al. RNA Sequencing Reveals Novel Transcripts from Sympathetic Stellate Ganglia During Cardiac Sympathetic Hyperactivity. Sci Rep. 2018 Jun 5;8(1):8633. **(3)** Kung GL, et al. Microstructural Infarct Border Zone Remodeling in the Post-infarct Swine Heart Measured by Diffusion Tensor MRI. Front Physiol. 2018 Aug 22; 9:826.
Training/Skills that will be acquired by the student: optical chromatography technique, optical imaging, molecular biology (gene expression, western blot, PCR, immunocytochemistry) and histology.
Supervisor: and brief biography: Dr Kamalan Jeevaratnam (FHMS, Surrey); Dr Pradeep Rajendran (University of California Los Angeles); Prof Kalyanam Shivkumar (University of California Los Angeles)
Department: Preclinical Veterinary Sciences, Faculty of Health and Medical Sciences

A7 Investigating the role of the sigma-1 receptor for cardiac protection

Abstract
Given the prevalence and severity of CVD, and the need for improved treatment options, efforts have been made to find novel pharmacological agents without adverse side effects. Scientists have searched an array of non-receptor channel constituents and ion channels to target for the treatment of disease. One such example is the Sigma receptors (Sig-Rs), which are ligand-gated chaperone proteins found throughout the central nervous system (CNS) and peripheral organs. While Sig-1Rs have been extensively studied in the brain, they are a ubiquitously-expressed protein. Sig-1Rs have been found to be present in multiple tissues in addition to the CNS, including the heart. It is interesting to note that Sig-1R protein levels are higher in heart tissue than brain tissue in rats. Furthermore, the various ion channels that Sig-1Rs have been shown to interact with are also present in the heart. This leads to the hypothesis that Sig-1R may play a role in the cardiovascular system. Given the neuroprotective role of Sig-1Rs in the nervous system, we can hypothesise that the Sig-1R may play a cardio-protective role as well. The primary aim of this project is to elucidate the electrophysiological and molecular features arising from selectively targeting the cardiac Sig-1R, and determine if manipulation of this receptor may confer protection of cardiomyocytes. We will assess for cardiac action potential activation and recovery using loose patch clamp and sharp electrode techniques. Calcium homeostasis properties will be assessed using fluorescence imaging, whilst molecular clarification will involve gene and protein expression analysis using gene card and western blots respectively.
References: (1) Alam S, et al (2017). Sigmar1 regulates endoplasmic reticulum stress-induced C/EBP-homologous protein expression in cardiomyocytes. *Biosci Rep* **37 (2)** Bers DM (2008). Calcium Cycling and Signaling in Cardiac Myocytes. *Annu Rev Physiol* **70,** 23–49. **(3)** Bhuiyan MS et al (2009). Stimulation of Sigma-1 receptor signaling by dehydroepiandrosterone ameliorates pressure overload-induced hypertrophy and dysfunctions in ovariectomized rats. *Expert Opin Ther Targets* **13,** 1253–1265.
Training/Skills that will be acquired by the student: electrophysiology – microelectrode technique, optical imaging, molecular biology (gene expression, western blot, PCR, immunocytochemistry) and tissue culture.
Supervisor (s): Dr Kamalan Jeevaratnam (FHMS, Surrey); Dr Rebecca Lewis (FHMS, Surrey) and Dr Peter McCormick (Queen Mary, London)
Department(s): Preclinical Veterinary Sciences

A8 'All or none' OR 'All or some' – elucidating the gating kinetics of the sodium channel in ageing

Abstract

Ion channels present within all cell plasma membranes, are responsible for key regulatory functions central to cellular homeostasis. These channels can generate electrical activity through selective permeability of chemical ions – essentially a channel current (I_c). The sodium channel plays a key role in the initiation of an action potential and is typically thought to have an 'all or none' function that generates the sodium current (I_{Na}). This means that the channel's gating kinetics ensure that it is either open or closed entirely with no possibility of partial opening or closure (known as a sub-conductance). More recently, there is evidence to suggest that the gating kinetics of the sodium channel may actually allow for partial opening or closure, giving rise to the term late sodium current (I_{NaL}). The infrequency of observation of these subconductances using traditional electrophysiological techniques could be due to the rapid inactivation of the channel. In this proposal we will utilise mathematical modelling techniques to investigate the gating kinetics and assess the temporal variation (i.e ageing) of the sodium channel. We aim to determine if temporal variations allow for changes in gating kinetics and if such altered gating kinetics can be resolved through electrical stimulation. We will use whole cell patch clamp to iteratively validate and refine the computational model.

References (1) Chadda KR, Jeevaratnam K, et al. Sodium channel biophysics, late sodium current and genetic arrhythmic syndromes. Pflugers Arch. 2017 Jun; 469(5-6):629-641. **(2)** Jeevaratnam K, Chadda KR, et al. Ion channels, long QT syndrome and arrhythmogenesis in ageing. Clin Exp Pharmacol Physiol. 2017 Dec; 44 **(3)** Jeevaratnam K, Chadda KR, et al. Cardiac Potassium Channels: Physiological Insights for Targeted Therapy. J Cardiovasc Pharmacol Ther. 2018 Mar; 23(2):119-129.

Training/Skills that will be acquired by the student: electrophysiology – microelectrode technique, optical imaging, computational modelling

Skills/qualifications/interests expected of potential student: computational modelling

Supervisor (s) and brief biography: Dr Kamalan Jeevaratnam (FHMS, Surrey); Dr Rebecca Lewis (FHMS, Surrey) and Prof Hengghui Zhang (School of Physics and Astronomy, University of Manchester)

Department(s): Preclinical Veterinary Sciences, Faculty of Health and Medical Sciences

A9. The role of oxidative stress and NADPH (Nox) enzymes in cardiovascular dysfunction during ageing

Abstract

Cardiovascular diseases are the number one cause of death worldwide and ageing is a major risk factor. The causes for ageing-associated cardiac and vascular dysfunction are multi-faceted but a key pathological mediator is the oxidative stress due to excessive reactive oxygen species (ROS) generated from the cells. Cellular ROS are mainly generated by enzymatic reactions. However, many enzymes generate ROS as their by-product as they perform biochemical oxidation to maintain cell activity. Therefore targeting these enzymes to control ROS production would inevitably compromise the physiological oxidation. One particular class of ROS generating enzymes are NADPH oxidases (Nox). Nox enzymes are the only proteins in the body that produce ROS as their sole function and thus can be targeted without compromising normal cell activity. Recently the Nox enzyme has generated intense interest as a specific molecular target for controlling ROS in a variety of the ageing- associated diseases and several small molecule Nox inhibitors are being developed. Seven Nox subtypes have been found to exist in the body. Nox2 and Nox4 have been shown to contribute to oxidative damage and vascular and cardiac dysfunction. However, how Nox subtypes specifically contribute to ageing heart and vasculature dysfunction is poorly understood, in particular molecular mechanisms and translational control. This is the first study to examine the role of Nox subtypes in contributing to cardiac and vascular ageing and dysfunction. We will use Nox2 and Nox4 knockout mice, in comparison with the wild-type mice, during ageing, to investigate effect of Nox2 and Nox4 deletion on cardiac and vascular function, and the underlying mechanisms. Cardiac hypertrophy, apoptosis and fibrosis, vascular endothelial dysfunction and remodelling and their correlation with ROS generation will be examined respectively in heart and aortic tissue. Several key transcription factors will be examined and microRNA involved will be identified to gain molecular insight. The outcome of this project will not only uncover molecular mechanisms for oxidative damage in cardiovascular ageing, but also inform the application of subtype-specific Nox inhibitors for controlling ageing associated cardiovascular diseases in the future. The project involves an integrated research approach involving both in vivo and ex vivo models with a wide range of techniques and will provide an excellent training opportunity for a PhD student

Training/Skills that will be acquired by the student: electrophysiology, histopathology, luminescence, molecular techniques, gene knockout/siRNA, next generation sequencing**,** bioinformatics

Supervisor (s) and brief biography: Dr Richard C Wu and other academic colleagues

Department(s): Biochemical Sciences, Cardiovascular research group

A10 Macrovascular complications and co-morbidity in T2DM: a comparison of two national primary-care datasets in England

Abstract

Diabetes is a disease that increases the risk of many other conditions that indirectly reduce survival. These include macrovascular and microvascular complications of diabetes as well as associated co-morbidities. Macrovascular disease is the primary cause of death in diabetes and data from UK has shown that it is two to four times more likely to occur in individuals with diabetes than in those without. The intention, for validation purposes, is to compare the diabetes population recorded in Clinical Practice Research Datalink (CPRD) with the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC).

Primary objective

To compare the cohorts of CPRD and RCGP RSC with respect to the prevalence of established cardiovascular disease (peripheral or coronary artery disease and/or one or more major adverse cardiovascular events) in T2DM.

Secondary objectives

i) To compare the cohorts of CPRD and RCGP RSC with respect to the prevalence of co-morbidities in association with T2DM (the Charlson co-morbidity index)

ii) Comparison (between CPRD and RCGP RSC datasets) of Cox proportional hazard models of survival of T2DM

Methodology A repeated cross-sectional study of complications of diabetes and a retrospective cohort study of major cardiovascular events or death using longitudinal data from the CPRD and RCGP RSC databases.

Outcomes The primary outcome measure of the study is the comparative prevalence of macrovascular disease in patients with T2DM in 2007 and in 2017. These include: Non-fatal MI, Non-fatal stroke, heart-failure, and surgical or percutaneous coronary revascularization procedure - as a proxy for unstable or incapacitating angina.

References:

McGovern A. *et al*., *BMJ Open* 2016; 6:e012801 doi:10.1136/bmjopen-2016-012801

Correa A. *et al*., *BMJ Open* 2016; 20;6(4):e011092

Woodmansey C*. et al*., *Diabetes Care*. 2017 Aug 31. pii: dc170542. doi: 10.2337/dc17-0542.

Davis MJ et al, Diabetologia, 2018 Oct 05, https://doi.org/10.1007/s00125-018-4729-5

Training/Skills that will be acquired by the student: Epidemiology, biostatistics, large dataset analysis

Supervisor (s) and brief biography:

Dr Ben Field, graduated in medicine with distinction from St Bartholomew's Hospital, London, in 1997. After specialist training at Guy's and St. Thomas' hospitals, he joined Imperial College London as an MRC clinical research training fellow, obtaining a PhD in 2009 for research into the neuroendocrine control of appetite, energy expenditure and insulin secretion. He is actively involved in research at SaSH and Imperial College, and is an honorary clinical senior lecturer at Imperial College London.

Dr. Martin Whyte, Clinical Senior Lecturer, Dr Whyte trained in medicine at King's College Hospital, qualifying in 1998. During my postgraduate medical training I undertook a PhD at Guy's & St. Thomas'

Hospital (University of London) examining the metabolic effects of insulin in critical illness. I then competed my specialist training (CCT) in Diabetes & Endocrinology and General Medicine in 2010. Since 2012 I have combined my NHS Consultant work with that of a Clinical Senior Lecturer at The University of Surrey.

Dr Uy Hoang, is a research fellow working within the Clinical Informatics & Health Outcomes Research Group in the Section of Clinical Medicine Ageing. Alongside specialist medical training in public health at the Oxford Deanery, he also has a doctorate in clinical epidemiology from the Institute of Psychiatry at King's College and a Masters in Public Health from Yale University. His research interests lie around the use of large, routinely collected datasets to study the occurrence and management of chronic physical and mental illness.

Prof Michael Feher, is a Consultant Physician in Diabetes & Clinical Pharmacology and Clinical Lead for lipid, diabetes and hypertension services at Chelsea and Westminster Hospital. He developed and leads unique specialist lipid and diabetes services including lipid clinics in adults and family lipids (joint with paediatrics), new diabetes therapies, liaison-psychiatry-diabetes, and diabetic hypertension

Dr Neil Munro is visiting professor of primary care diabetes in the department of clinical and experimental medicine, University of Surrey. He was an associate specialist in diabetes at the Chelsea and Westminster hospital, London from 1998 until 2015 and has worked in specialist hospital based diabetes clinics since 1985. He was also a general practitioner in Surrey from 1984 until 2013 and provided diabetes services to patients of the practice during that time.

Prof Simon de Lusignan, is a senior academic GP and Professor of Primary Care and Clinical Informatics; Chair in Health Care Management; and Head of Department of Department of Clinical and Experimental Medicine at University of Surrey.

Department(s): Clinical & Experimental Medicine

A11 Evaluating the impact of vitamin K antagonists (VKA) and non-vitamin K oral anticoagulants (NOAC) on vascular ageing

Abstract

The major challenges of today is cardiovascular ageing. One of the key characteristics of vascular ageing are arterial calcification, stiffening, and arterial hypertension. Vitamin K antagonists (VKA) have been used for a long time as long-term blood thinners in patients with atrial fibrillation, pulmonary embolism, and deep vein thrombosis. However, bleeding complications are frequent and VKA may also interfere with the carboxylation of matrix gla protein (MGP), which is important for preventing calcification of arteries. Hence, VKA may promote arterial calcification and ageing. More recently, non-vitamin K oral anticoagulants (NOAC) have been introduced, are now widely used, and act via direct effects on clotting factors, in particular though inhibition of factor Xa and thrombin. It is the overall **objective** of the project to evaluate the effect of VKA and NOACs on the progression of vascular ageing. Specifically, the project aims at evaluating the trajectories of (systolic) blood pressure increase over time in primary care patients as compared to patients without oral anticoagulation. Using the RCGP-RSC database with almost 4 Million patients and 400 practices, the **methodology** will include a retrospective cohort study evaluating the trajectories of blood pressure (primary outcome) in patients with VKA, NOACs, and patients without anticoagulation. The secondary outcomes include first diagnosis of macrovascular cardiovascular diseases (coronary, peripheral, and cerebrovascular artery disease) and major adverse cardiovascular events including myocardial infarction, revascularization, stroke, amputation, cardiovascular death. Tertiary outcomes relate to microvascular disease. Covariates will include blood pressure medication and co-morbidities.

References: McGovern A. et al., BMJ Open 2016; 6:e012801 doi:10.1136/bmjopen-2016-012801; Correa A. et al., BMJ Open 2016; 20;6(4):e011092; Woodmansey C. et al., Diabetes Care. 2017 Aug 31. pii: dc170542. doi: 10.2337/dc17-0542; Heiss C. et al. Experimental Gerontology 2018

Training/Skills that will be acquired by the student: Epidemiology, biostatistics, large dataset analysis

Supervisor(s) and brief biography:

Prof Christian Heiss is a Professor of Cardiovascular Medicine at the University of Surrey and Honorary Consultant the Surrey and Sussex Healthcare NHS Trust. He is an interventional angiologist and cardiologist and has previously headed Vascular Medicine at the University of Duesseldorf, Germany. His research interests include basic mechanisms of vascular homeostasis and human interventions for improvement of cardiovascular health and healthy aging.

Prof Simon de Lusignan, is a senior academic GP and Professor of Primary Care and Clinical Informatics; Chair in Health Care Management; and Head of Department of Department of Clinical and Experimental Medicine at University of Surrey. He is also the Medical Director of the Royal College of General Practitioners Research Surveillance Centre (RCGP-RSC)

Department(s): Department of Clinical and Experimental Medicine

A12 The role of exosomes in ageing and myocardial infarction

Abstract

The impact of this work will reveal a novel and exciting avenue for regenerative medicine and stem cell research, termed acellular therapy. Over the last decade, regenerative medicine has come to the forefront of the treatment of myocardial infarction. Unlike other major organs, the heart has very little regenerative capacity under physiological conditions, at approximately 1% turnover of newly formed cardiomyocytes. This rate does not increase under pathological conditions including myocardial infarction, consequently leading to end-stage heart failure. In addition, the transplantation of stem cells that are of mesenchymal origin or even derived endogenously from the heart, have a very limited capacity to differentiate to cardiomyocytes after myocardial infarction. However, functionally, the transplantation of stem cells improves cardiac function and decreases the pathology of myocardial infarction. This has lead to the hypothesis that these cells improve cardiac function after myocardial infarction by a paracrine effect. Here we will investigate one of these novel paracrine factors called exosomes. In addition, ageing is the biggest factor that predisposes people to myocardial infarction. To this end, our first objective is to harvest exosomes from young and aged induced pluripotent stem cells, where we will perform a microarray analysis of genes to identify major targets that differentiate between young and aged exosomes. Our second objective will be to co-culture young and aged exosomes with IPS cells to investigate their ability to facilitate direct differentiation and differentiation to the tri-lineage. Our third objective will be to test the viability using apoptosis assays and proliferation of IPS cells when treated with young and aged exosomes. Having identified the potential targets between young and aged exosomes, we will use CRISPR-Cas technology to perform genome editing to revert aged exosomes to young exosomes where differentiation, proliferation and apoptosis will be investigated. Our next objective will be to observe the metabolic effects of IPS cells when co cultured with young or old exosomes. We hypothesise that there will be significant alterations in the metabolic machinery when cultured with aged exosomes which may purpose a mechanism for the lack of their regenerative capacity. Finally the electrophysiological properties of IPS cells will be compared using next-generation momochromator technology. Here, this optical device utilises light-induced electrophysiology to yeild high-quality data on cardiac voltage-gated channels. This technique has a comparable sensitivity, prescioin and reliability compared to traditional voltage clamp recordings. We will identify any such differences in the electrophysiologocal preperties of IPS cells when incubated with young or old exosomes. **Our data will reveal a thorough investigation of exosomes which will lead to a deeper understanding of how ageing effects this. This research project will lead to highly innovative findings with a high impact that will reinvigorate the regenerative medicine field. This work will show great relevance to current applications including ageing and cardiovascular disease.**

References:

1. **Senescent, dysfunctional human cardiac progenitor cells (CPCs) accumulate in the aged heart and elimination of senescent cells enhances CPC activation and cardiomyocyte proliferation in aged mice**. Lewis-McDougall FC, **Ruchaya PJ**, Domenjo-Vila E, Teoh TS, Prata L, Cottle BJ, Clark JE, Punjabi PP, Awad W, Torella D, Tchkonia T, Kirkland JL, Ellison-Hughes GM. (Preprint, BioRxiv: doi.org/10.1101/397216).
2. **The Transplantation Of Pw1^{+}/Pax7^{-} Skeletal Muscle-derived Interstitial Progenitor Cells (PICs) Improves Cardiac Function In Myocardial Infarction Mice. Ruchaya PJ** et al. (2018)**.**

In preparation, JAAC

3. **GFRA2 identifies cardiac progenitors and mediates cardiomyocyte differentiation in a RET-independent signaling pathway.** Hidekazu Ishida, Rie Saba, Ioannis Kokkinopoulos, **Prashant J. Ruchaya**, Sonja Nowotschin, Manabu Shiraishi**,** Duncan Miller, Stephen Harmer, Ariel Poliandri, Shigetoyo Kogaki, Leo Dunkel, Andrew Tinker, Anna-Katerina Hadjantonakis, Keiichi Ozono, Ken Suzuki, and Kenta Yashiro. *Cell Reports, 26;16(4), (2016) IF 7.8*
4. **Single-Cell Expression Profiling Reveals a Distinct Character of *Tbx5*-expressing Cardiac Precursor Cells in the Early Mouse Embryo.** Ioannis Kokkinopoulos, Hidekazu Ishida, Rie Saba, **Prashant J. Ruchaya**, Claudia Cabrera, Monika Bozek, Michael Barnes, Anna Terry, Masahiro Kaneko, Yasunori Shintani, Steven Coppen, Hidetaka Shiratori, Torath Ameen, Charles Mein, Hiroshi Hamada, Ken Suzuki, and Kenta Yashiro. *PLoS One. (2015) IF 3.23*

Supervisor:

Dr: Prashant Jay Ruchaya- I carried out my PhD at the University of Bristol, during this time, my main area of research was the investigating the effects of heart failure on the neuroendocrine system. I carried out a whole systems physiological approach where working on rodents, I performed surgical procedures to induce heart failure, perform brain microinjections of drugs/viruses by stereotaxic surgery. Recording chronic blood pressure and heart rate by implanting telemetry devices. Using pressure-volume catheters inserted into the left ventricle for measurements. After completing my PhD in 2011, I spent a year in Florida, USA, followed by a year in Seville, Spain and three years in Sao Paulo, Brazil. All of these research positions involved me carrying out work on stem cell biology and cardiovascular disease. Prior to starting my position at the University of Surrey this year, I worked at King's College London for almost three years. Most of my research involved animal models of heart failure and regenerative medicine where I transplanted stem cells after injury to the hearts of rodents. My major focus was to assess the effects of ageing on stem cell potency. Post recovery, assessments were conducted using echocardiography and PET imaging. To date, I intend on continuing my research in effective ways of harvesting regenerative potential of stem cells.

Department(s): School of Veterinary Medicine, University of Surrey.

B. Infection and Immunity

B1 Single cell transcriptional approaches to understanding antibody class switching.

Abstract
Antibodies are protein molecules of immense importance to our health and to the pharmaceutical industry. Textbook theory is that our immune systems can evolve a useful, and high affinity IgM antibody Fv region, then that same Fv can be used with different Fc regions to change the class of the antibody in order to have the same binding capability but having different functions. Recent data in our lab has highlighted that our understanding of class switching events is inadequate, and that there is huge potential for improved vaccine design and immunotherapeutics if we move the focus away from IgG_1 action to include other significant isotypes and subclasses of antibody.
The main objective of this project is to investigate what factors can affect class switching in human B cells. This will be done by culturing the cells with different cocktails of growth factors/cytokines and seeing the effect on class switching and phenotype (by FACS). When robust methods of inducing class switching are defined we will follow up by studying the transcriptome changes in response to class switching (by single cell methods) in order to understand the mechanisms involved.
Training/Skills that will be acquired by the student:
Single cell transcriptional analysis of immune cells (using microfluidics), PCR, analytical skills, FACS analysis, Cell culture, possibly also antibody cloning and analysis
Skills/qualifications/interests expected of potential student:
Understanding of B cell immunology. Comfortable with Excel spreadsheets. Aseptic technique. Interest/competence in learning R and other bioinformatics skills is an advantage
Supervisor (s) and brief biography:
Professor Deborah Dunn-Walters is Head of Section of Immunology, and Research Director of the School of Biosciences and Medicine. She advises the UKRI BBSRC Bioscience for Health Strategy panel, the MRC Eminent advisory board and she is a Trustee, and chair of the Research Grants committee for the Dunhill Medical Trust. Her research interests are in the study of B cell development and immune senescence and she is an expert on immunoglobulin repertoire analysis.
Department(s): School of Biosciences and Medicine - Immunology Section

B2 Cytosolic sensing of vaccinia virus: towards enhancing the immunogenicity of vaccine vectors

Abstract

Viruses must face an arsenal of immune sensors aimed at detecting their presence. All viruses must evade RNA sensors, but DNA viruses must in addition contend with DNA sensing pathways [1]. Vaccinia virus (VACV) – the virus used to vaccinate and eradicate smallpox – is a large DNA virus that replicates exclusively in the cell cytosol [2]. The interplay between VACV and cytosolic DNA sensing is largely unknown and only recently have we begun to identify the molecules in our cells that are key in shaping the anti-viral response to VACV [3,4]. We have recently identified a novel pathway recognising VACV in macrophages that is dependent on both STING and IRF3, two pivotal players in innate immune sensing, and that operates in the endosome (unpublished). This project will characterise this pathway in more detail using CRISPR/Cas-9 knock-out cells and pharmacological inhibitors of the endosomal pathway and will determine the molecular signatures in the virus that mediate its recognition. Given the role of macrophages as professional APC this project has the potential to uncover the mechanisms underpinning VACV immunogenicity and hence their therapeutic manipulation in vaccinology.

References:

1. Chen, Q., Sun, L. & Chen, Z.J. Regulation and function of the cGAS-STING pathway of cytosolic DNA sensing. *Nat Immunol* **17**, 1142-1149 (2016).
2. Smith, G.L*., et al.* Vaccinia virus immune evasion: mechanisms, virulence and immunogenicity. *J Gen Virol* **94**, 2367-2392 (2013).
3. Georgana, I., Sumner, R.P., Towers, G.J. & Maluquer de Motes, C. Virulent poxviruses inhibit DNA sensing by preventing STING activation. *J Virol* (2018).
4. Meade, N*., et al.* Poxviruses Evade Cytosolic Sensing through Disruption of an mTORC1-mTORC2 Regulatory Circuit. *Cell* **174**, 1143-1157 e1117 (2018).

Supervisor (s) and brief biography:

Dr Carlos Maluquer de Motes is a Lecturer in Virus-Host Interactions at the University of Surrey since 2014. Before he trained at Cambridge University and ICL. His group studies the antiviral immune response with an emphasis on nucleic acid sensing and uses large DNA viruses such as poxviruses to understand how this response is mounted.

Prof David J Blackbourn is Professor and Head of the School of Biosciences and Medicine at the University of Surrey. Prof Blackbourn has published 75 papers on virology and immunology. His major interest is in how viruses cause disease and modulate the immune response.

Department(s):

Department of Microbial Sciences, School of Biosciences and Medicine

B3 Role of commensal bacteria as beneficial immunomodulators during tuberculosis infection

Abstract

Tuberculosis (TB) is a chronic infectious disease that is still endemic in many countries around the world. The *Mycobacterium tuberculosis* complex (MTC) is the causative agent of TB and affects animals and humans, resulting in devastating consequences in global economy and public health. How to increase the efficacy of control measures against MTC remains a goal of utmost importance. A novel strategy that this project proposes is the beneficial manipulation of the host-commensal bacteria alliance against TB infection. This innovative approach requires a detailed understanding of how commensal bacteria and MTC compete for macrophages at the initial stages of the infection process and during infection. Macrophages are the optimal niche that MTC requires for survival, replication and dissemination. Therefore, we aim to understand and determine the mechanisms that typical commensal bacteria such as lactobacilli utilize to display antagonistic properties associated with the inhibition and elimination of TB infection. Firstly, we propose to identify the mechanisms that lactobacilli previously isolated from animals and humans, utilize to inhibit MTC. Secondly, we will conduct competition assays between lactobacilli and MTC using macrophages to determine the phagocytic response and the type of cell death –apoptosis vs necrosis- that our lactobacilli activate in the presence of MTC. Understanding how lactobacilli inhibit MTC and module beneficial responses in macrophages will provide a unique opportunity to learn about new alternatives for anti-TB therapies.

References:

Stedman A, Maluquer de Motes C, Lesellier S, Dalley D, Chambers M, **Gutierrez-Merino J**. **2018**. Lactic acid Bacteria isolated from European badgers (*Meles meles*) reduce the viability and survival of Bacillus Calmette-Guerin (BCG) vaccine and influence the immune response to BCG in a human macrophage model. *BMC Microbiol.* 18(1):74.

Mohlopheni JM, **Martinez FO**, Plüddemann A, Gordon S. **2018**. Macrophage heterogeneity in the immunopathogenesis of tuberculosis. *Front Microbiol*. 9:1028.

Supervisor (s) and brief biography: This project will be supervised by Dr Jorge Gutierrez-Merino (JGM) in collaboration with Dr Fernando Martinez Estrada (FME). JGM is a Lecturer in Food Microbiology at University of Surrey (UoS) and has attracted funding as PI from Royal Society and Morris Animal Foundation, a prestigious American charitable trust that aims to improve the health and welfare of animals. Jorge has a domain expertise in the isolation and molecular characterization of commensal bacteria. He has also been trained in many applied microbiology techniques including cloning, transcriptional analysis and genome sequencing. His lab has all the bacterial strains and the methodologies required to study the mechanisms that commensal bacteria use to inhibit pathogenic mycobacteria. FME was a senior research associate at Oxford University before being appointed Lecturer in Innate Immunology at UoS. He has been well-trained in the transcriptome of innate immune cells to understand how to inactivate and reprogramme them, a fundamental question in inflammatory medicine. His area of expertise is functional regulation of macrophages, including isolation-culture, gene and proteomics signatures, microarrays and proteomics, all of which are complemented with conventional histology and modern techniques such as multiple immunofluorescence histology, multiple FACS staining and Cytof.

Department(s): Nutritional Sciences and Biochemical Sciences, School of Biosciences and Medicine, UoS

B4 Role of drug synergy in preventing development of drug-resistance in bacteria.

Abstract

Objectives: When genetically identical drug-sensitive bacteria are treated with an antibiotic, although 99.99% of cells are killed, there is always a small number of cells that survivor the killing action of the antibiotic that we call persisters. These survivors are not genetically resistance but they are able to survive antibiotic and may be the progenitors of true genetic drug resistance. To combat the development of bacterial resistance, patients are often treated with multiple antibiotics which are thought to act in synergy to kill bacterial cells. However, the mechanism by which effective synergistic drug combinations work is far from clear. The objective of this project is to develop a mechanistic understanding of drug synergy in tuberculosis (TB) that may allow us to novel synergistic drug combinations to combat the development of drug resistance.

Methodology: In this project you will investigate how persistence to one antibiotic overlaps with persistence to another antibiotic in mycobacteria, the group of bacteria that cause tuberculosis. Cells will be treated with (1) antibiotic A, (2) antibiotic B, (3) antibiotic A + antibiotic B. We will investigate how the antibiotics synergize, for example whether combinations of antibiotics that act on the same target (e.g. cell wall) are better at killing persisters than antibiotics that act on different targets (e.g. cell wall and translation). In parallel, metabolomics approaches will be used to examine how the metabolism of bacteria is affected by the drugs and investigate the hypothesis that synergistic drugs work by attacking complementary metabolic pathways.

References:

Balaban, Nathalie Q., et al. "A problem of persistence: still more questions than answers?." Nature Reviews Microbiology 11.8 (2013): 587.

Basu P. et al, The anaplerotic node is essential for the intracellular survival of *Mycobacterium tuberculosis.* Journal of Biological Chemistry 2018: J. Biological Chemistry. RA118. 001839.

Training/Skills that will be acquired by the student: Microbiology, molecular biology, metabolomics

Skills/qualifications/interests expected of potential student: BSc level Biosciences.

How will this project build/enhance on research strengths of Surrey/SJTUMS and provide opportunities for further collaboration and research funding: Drug-resistance is a priority for both institutes and a target for many funding agencies.

Supervisor(s): Dr. Suzie Hingley-Wilson and Prof. Johnjoe McFadden

Department(s): Microbial Sciences, FHMS

B5 Tuberculosis and the circadian clock

Abstract
Many of the biochemical, physiological, and behavioural processes of most organisms are driven by intrinsic circadian ('about a day') clocks, which are synchronised to daily cycles in the external environment. Macrophages have their own functional circadian clock. There is increasing evidence that the recognition of bacterial and viral pathogens is regulated by the macrophageintrinsic circadian clock. The causative agent of TB, *Mycobacterium tuberculosis (Mtb),* the world's number one infectious killer, has co-evolved with humans for approximately 70,000 years. It is emerging that that synchrony between host and pathogen rhythms is critical to disease progression, and the question arises whether this is also true for *Mtb.* This is especially topical, because *Mtb* resides in macrophages and is able to persist in the human host for decades. TB is thus regularly exposed to the rhythmic environment of the human immune system. As adapting to the human macrophage niche is critical to the survival and overall success of *Mtb*, this leads to the question: **Has *Mtb* evolved its own mechanisms to co-ordinate its attack of and survival within the circadianhost?** This project will be the first to test the hypothesis that **circadian rhythms are a critical factorin the interaction between macrophages and *Mtb.*** *Understanding the impact that circadian rhythms have on the ability of Mtb to invade and/or survive within the host is likely to inform therapeutic strategies, from novel drug design to the chronotherapeutic administration of current anti-TB drugs and vaccines.*

Methodology and Timescale
Year 1: How does the circadian rhythm impact on *Mtb* infection?
Using established methods the macrophage cell lines will be synchronised. Synchronisation will be confirmed by measuring the oscillation of key clock genes by QRT-PCR. Mycobacterial infection assays will be performed in synchronised macrophage cells at different times in the circadian cycle and monitored using flow cytometry and culture. This work will be confirmed in the pathogen once the student is trained at containment level 3. CRISPR knock down of core clock genes will be performed to explore the impact of disrupting the circadian rhythm of Mtb.

Year 2: Does *Mtb* modulate the circadian clock in macrophages to facilitate intracellular survival?
Transduced primary and cell line macrophages with a lentiviral luciferase reporter that is under control of a core clock gene promoter will be used for real-time reporting of circadian dynamics. This strategy will be used to test whether Mtb infection impacts on the circadian rhythm of the macrophage host cells. To determine whether circadian modulation occurs at the transcriptional level in response to infection we will measure the differential gene expression profile by RNA-seq of synchronised macrophages infected with Mtb or uninfected at different circadian times.

Year 3: Does Mtb have its own rhythm?
Mycobacterial cultures will be synchronised using standard methods in a chemostat and then transcriptomics will be performed to test for circadian patterns of expression.
Training: The student will receive training in microbiology, molecular biology (including CRISPR), and eukaryotic cell culture and flow cytometry. The student will also receive training in how to work at Containment level 3 suite. Training in statistical and computational approaches that will support the

aims of the project will also.

Most Relevant Publications: Prior et al, (2018) Timing of host feeding drives rhythms in parasite replication, PLOS Pathogens 14 (2) e1006900 DOI: 10.1371/journal.ppat.1006900; Keller et al, (2009). A circadian clock in macrophages controls inflammatory immune responses. PNAS;106 (50):21407-12. doi: 10.1073/pnas.0906361106.

Supervisors and webpages: Dany Beste (Microbial Sciences) https://www.surrey.ac.uk/people/dany-beste; Daan Van Der Veen (Dep. Biochemistry) https://www.surrey.ac.uk/people/daan-van-der-veen

B6 Last mile for lymphatic filariasis elimination in Sri Lanka

Abstract
The Global Program for Eliminating Lymphatic Filariasis (GPELF) was launched in 2000 by WHO, and Sri Lanka was one of the first countries initially endemic that has been certified as having eliminated LF as a public health problem. With a few hotspots remaining, the Sri Lanka LF control program is close to achieving true elimination in the coming years. The purpose of this PhD project will be to work alongside the Ministry of Health in Sri Lanka during the last few years of the control program, collecting additional data where needed and providing robust analytics and recommendations. Some of the key questions are: a) What is the spatial distribution of the last LF cases (human and mosquito) in Sri Lanka?; b) How well does mosquito infection prevalence predict the location of the remaining LF cases?; c) What factors contribute to maintain low endemicity in the last mile?; d) How can true LF elimination be assessed?
The student will be responsible for the data analysis and developing mathematical modelling tools, based on previous work from Dr. Prada and colleagues in LF and other neglected tropical diseases [1,2,3] to help support the LF control program.
References:
[1] Parasit Vectors. 2018 Jan 8;11(1):21; [2] Trans R Soc Trop Med Hyg. 2018 Aug 1;112(8):397-404; [3] Clin Infect Dis. 2018 Jun 1;66(suppl_4):S260-S266
Training/Skills that will be acquired by the student:
cross-sectional epidemiological and mathematical modelling skills
Skills/qualifications/interests expected of potential student:
Interests in public health, epidemiology and mathematical modelling; willingness to travel
Supervisor: Dr. Joaquin M. Prada, lecturer in veterinary epidemiology with a research focus on mathematical models of infectious diseases in humans and animals, and a particular emphasis on helping policy decision-making in control and elimination programs.
Department(s): Veterinary Epidemiology and Public Health

C. Molecular Biology and Stem Cell Biology

C1 Understanding how altered translation contributes to neurodegenerative diseases using novel stem cell models

Abstract

Neurodegenerative disorders (NDs) affecting the ageing population are characterized by the loss of specific cells. In response to stress, such as neurodegeneration, cells can pause protein synthesis, or translation, by storing messenger RNAs away in cellular compartments called stress granules. This defense mechanism allows cells to survive by limiting the use of energy, pausing general translation while allowing the specialized translation program essential to stress recovery. If prolonged, this stress can lead to cell toxicity and death. Neurons are highly specialized cells reliant on accurate control of translation to maintain their unique functions throughout the lifespan. Not surprisingly the dysregulation of the translation pathway is central to the pathogenesis of several NDs. Furthermore, restoring translation activity in model systems can decrease the severity of disease. Therefore the regulation of translation is a promising therapeutic target for treating treatment of NDs. To understand of how translation regulation affects the loss of neuronal functions, we will use novel genetically engineered isogenic human stem cell lines to generate neuronal populations representative of Alzheimer's disease (AD) and Parkinson's disease (PD) which cover >70% of NDs patients. In control and disease cells, we will 1-measure global translation activity at the single cell level and characterise the presence of stress granules, 2-dissect the stress-specific translation program triggered by the cell and 3-measure the impact of the NDs on the metabolism and phenotype of ageing neurons. This work will provide new leads for the therapeutic restoration of translation in NDs of the ageing population.

References:

In addition to those in CV: mRNA circularization by METTL3-eIF3h enhances translation and promotes oncogenesis. Choe J et al. *Nature* 2018. 561(7724):556-560. Disturbances of sleep quality, timing and structure and their relationship with other neuropsychiatric symptoms in Alzheimer's disease and schizophrenia: insights from studies in patient populations and animal models. Winsky-Sommerer et al, *Neurosci Biobehav Rev* 2018 S0149-7634(17)30879-5.

Training/Skills that will be acquired by the student: RNA biology, immunofluorescence microscopy, cell culture (stem cells).

Supervisor (s) and brief biography:

Dr Nicolas Locker is an expert in RNA biology and diseases; his work has been published in Nature, Nucleic Acids Research, mBio; research in his lab is supported by funding from the Medical Research Council and Biotechnology and Biological Sciences Research Council.

Dr Raphaelle Winsky-Sommerer's research focuses the relationship between chronic stress, neurodegeneration and sleep disturbances; her work has been published in Science, Current Biology, Journal of Neuroscience; research in her lab has been supported by funding from the Biotechnology and Biological Sciences Research Council, pharmaceutical industry and philanthropic gift.

Departments: Microbial Sciences / Clinical and Experimental Medicine

C2 The development of improved bio-engineered expression cassettes for gene therapy of haemophilia A

Abstract

Haemophilia is an attractive target for gene therapy. Adeno-associated virus encoding factor (F) IX has been shown to be effective for the treatment of haemophilia B and is being evaluated in on-going clinical trials 1. However, haemophilia A, poses a more complex but tractable challenge due to the distinct molecular and biochemical properties of FVIII. These include the larger size of the cDNA the significantly lower expression levels and short half-life of FVIII. Bioengineered expression cassettes encoding novel forms of FVIII have been designed and tested with the aim of improving properties such as biosynthesis, secretion efficiency, functional activity and plasma half-life. It is known from attempts to bioengineer high expressing FVIII cell lines for bio-manufacturing recombinant FVIII that newly synthesised FVIII misfolds in the endoplasmic reticulum leading to activation of the unfolded protein response (UPR), oxidative stress and apoptosis. We recently developed a number of novel FVIII expression cassettes that direct significantly improved expression profiles. We would now like to extend these studies by engineering FVIII expression cassettes with potentially extended half-lives and determine whether these and our recently described bioengineered FVIII expression cassettes also reduce FVIII misfolding leading to reduced activation of UPR and cellular apoptosis.

References:

1. Shestopal et al J Thromb Haemost. 2017 15(4):709-720.
2. McIntosh et al Blood. 2013 121(17):3335-44.
3. Ward et al Blood. 2011 117(3):798-807.

John McVey is Professor of Cardiovascular Biology at the University of Surrey and holds an Honorary Professorship at University College London (UCL) and visiting Professorship at Royal Holloway, London.

He has authored or co-authored over 100 peer-reviewed papers and many book chapters in the area of blood coagulation and haemostasis. He has established an international reputation within the field of haemostasis and is regularly invited to review manuscripts for leading journals and grants for both national and international bodies. He is a communicating editor for Human Mutation and Thrombosis and Haemostasis as well as a member of the Editorial Board of the Journal of Thrombosis and Haemostasis and Arteriosclerosis, Thrombosis and Vascular Biology.

His research focuses on the regulation of blood coagulation and the role that coagulation factors play in normal physiology and in the pathophysiology of disease.

Department(s): Biochemical Sciences

C3 Functional analysis of stress-dependent RNA-enzyme interactions

Abstract

RNA-binding proteins (RBPs) play essential roles in the post-transcriptional control of gene expression with widespread implications in development and disease. The recent introduction of proteome-wide approaches has dramatically expanded the repertoire of proteins interacting with RNA, revealing many "unconventional" RBPs with other well-established functions, such as metabolic enzymes [1, 2]. Nevertheless, while the repertoire of RBPs is steadily increasing [2], little is known about the reconfiguration of the RNA-protein interactions upon stress and RNA-related functions of metabolic enzymes.

To address this lack of knowledge, we started to monitor the reconfiguration of the RNA-binding proteome (RBPome) upon environmental stress. we observed prime changes of RNA-association among a class of metabolic enzymes with roles in cancer and other diseases.

In this project, we aim to further characterise these stress-dependent enzyme-mRNA interactions by undertaking an in-depth functional analysis of a conserved RNA-binding enzyme acting in carbon metabolisms in yeast and human cells. Specifically, we aim

i) to comprehensively profile the RNA targets and proteins interacting of a selected enzyme in stressed and non-stressed cells. Therefore, we will implement formaldehyde-based crosslinking-immunoprecipitation (fRIP) followed by high-throughput RNA sequencing to identify RNA targets at a global level; and we will perform mass-spectrometry analysis to monitor the composition of RNA-enzyme complexes.

ii) to monitor the implications of enzyme-RNA interactions in gene expression, for enzyme activity and its consequences in stress adaptation. To achieve this, we will implement a range of biochemical and enzymatic assays, including mutational analysis in the RNAs and enzymes to study RNA binding properties, implications in post-transcriptional gene regulation and physiological impact.

Our research is expected to elucidate "moonlighting" functions of key metabolic enzymes and will likely uncover new principles for cellular stress adaptation. Since both, enzymes acting in carbon metabolism and the cell's response to stress are of considerable interest - ranging from improving fermentation processes in yeast which are relevant in the food and biofuel industry to the development of new strategies for cancer treatment in humans - our research could eventually generate economical and societal impact.

References

[1] Matia-González, A.M., Laing, E.E, Gerber, A.P. (2015) Conserved mRNA-binding proteomes in eukaryotic organisms. Nat. Struct. Mol. Biol. *22*(12), 1027-33.

[2] Albihlal, W.A., Gerber, A.P. (2018) Unconventional RNA-binding proteins: an uncharted zone in RNA biology. FEBS Lett. *592*(17), 2917-2931.

Training/Skills that will be acquired by the student:

Molecular cell biology, Biochemistry, global analysis of RNA-protein interactions (RIP/CLIP-seq), Bioinformatics

Skills/qualifications/interests expected of potential student:

Molecular Biology and Biochemistry skills. Good computational skills (Knowledge of R-package and programming would be plus but is not essential to project).

André Paul Gerber

Summary: André Gerber has long-standing expertise in RNA research with focus on RNA-binding proteins and non-coding RNA interaction networks and the translatome in health and disease. He published more than 50 peer-reviewed articles (including Science, PNAS, Genome Res., PLoS Biology, Nature Struct. Mol. Biol.) and was awarded several research grants (BBSRC, Leverhulme, SNF) on the theme. In 2017, he received a Wolfson Research Merit Award from the Royal Society.
Department(s): Microbial Sciences, School of Biosciences and Medicine, FHMS, University of Surrey

C4 Role of coagulation factors in modulating delivery of adenoviral gene therapy vectors

Abstract
Adenoviruses (Ad) are common pathogens. Gene transfer vectors based on Ad are used extensively in pre-clinical research and over 25% of clinical trials worldwide. In spite of this extensive utilization, the basic mechanisms that govern Ad infectivity remain poorly understood. Ad5 vectors delivered through the bloodstream show profound liver infectivity. In 2008 we defined a critical new function for the Ad5 hexon. Previously believed to be a structural protein with a passive role in Ad5-mediated infection, we showed that the Gla domain of coagulation factor (F)X binds to the hexon surface. The complex of Ad5:FX binds to hepatocytes through the FX serine protease domain which interacts with cell surface heparan sulphate proteoglycans. This critically important new information was a paradigm shift for Ad biology and the development and use of such viruses in pre-clinical and clinical settings. In this PhD project we will focus on the sequence requirements for FX binding to hexon. This will allow us to develop novel FX chimeras as retargeting strategies for the delivery of adenoviral vectors for gene therapy.

References (all co-authored by the Surrey lab and/or supervisor):

1. Ma et al PLoS Pathog. 2015 11(2):e1004673.
2. Baker et al Mol Ther. 2007 15(8):1410-6.
3. Duffy et al J Virol. 2011 85(20):10914-9.
4. Parker et al J Virol. 2007 81(7):3627-31.
5. Kritz et al Mol Ther. 2007 15(4):741-9.
6. Greig et al Mol Ther. 2009 17(10):1683-91.
7. Parker et al J Virol. 2009 83(1):479-83.
8. Waddington et al J Virol. 2007 81(17):9568-71.
9. Alba et al Blood. 2009 30;114(5):965-71.
10. Alba et al Blood. 2010 116(15):2656-64.
11. Parker et al Blood. 2006 108(8):2554-61.
12. Waddington et al Cell. 2008 132(3):397-409.

John McVey is Professor of Cardiovascular Biology at the University of Surrey and holds an Honorary Professorship at University College London (UCL) and visiting Professorship at Royal Holloway, London.
He has authored or co-authored over 100 peer-reviewed papers and many book chapters in the area of blood coagulation and haemostasis. He has established an international reputation within the field of haemostasis and is regularly invited to review manuscripts for leading journals and grants for both national and international bodies. He is a communicating editor for Human Mutation and Thrombosis and Haemostasis as well as a member of the Editorial Board of the Journal of Thrombosis and Haemostasis and Arteriosclerosis, Thrombosis and Vascular Biology.
His research focuses on the regulation of blood coagulation and the role that coagulation factors play in normal physiology and in the pathophysiology of disease.
Department(s): Biochemical Sciences

C5 The development of improved bio-engineered expression cassettes for gene therapy of haemophilia A

Abstract
Haemophilia is an attractive target for gene therapy. Adeno-associated virus encoding factor (F) IX has been shown to be effective for the treatment of haemophilia B and is being evaluated in on-going clinical trials 1. However, haemophilia A, poses a more complex but tractable challenge due to the distinct molecular and biochemical properties of FVIII. These include the larger size of the cDNA the significantly lower expression levels and short half-life of FVIII. Bioengineered expression cassettes encoding novel forms of FVIII have been designed and tested with the aim of improving properties such as biosynthesis, secretion efficiency, functional activity and plasma half-life. It is known from attempts to bioengineer high expressing FVIII cell lines for bio-manufacturing recombinant FVIII that newly synthesised FVIII misfolds in the endoplasmic reticulum leading to activation of the unfolded protein response (UPR), oxidative stress and apoptosis. We recently developed a number of novel FVIII expression cassettes that direct significantly improved expression profiles. We would now like to extend these studies by engineering FVIII expression cassettes with potentially extended half-lives and determine whether these and our recently described bioengineered FVIII expression cassettes also reduce FVIII misfolding leading to reduced activation of UPR and cellular apoptosis.
References (all co-authored by the Surrey lab and/or supervisor):

1. Shestopal et al J Thromb Haemost. 2017 15(4):709-720.
2. McIntosh et al Blood. 2013 121(17):3335-44.
3. Ward et al Blood. 2011 117(3):798-807.

John McVey is Professor of Cardiovascular Biology at the University of Surrey and holds an Honorary Professorship at University College London (UCL) and visiting Professorship at Royal Holloway, London.
He has authored or co-authored over 100 peer-reviewed papers and many book chapters in the area of blood coagulation and haemostasis. He has established an international reputation within the field of haemostasis and is regularly invited to review manuscripts for leading journals and grants for both national and international bodies. He is a communicating editor for Human Mutation and Thrombosis and Haemostasis as well as a member of the Editorial Board of the Journal of Thrombosis and Haemostasis and Arteriosclerosis, Thrombosis and Vascular Biology.
His research focuses on the regulation of blood coagulation and the role that coagulation factors play in normal physiology and in the pathophysiology of disease.
Department(s): Biochemical Sciences

C6 Stem cell ageing – characterization of the biophysical and molecular properties central to stem cell implantation

Abstract

Mechanisms underlying age-related deteriorations in cellular and tissue function, including increased incidences of cardiac arrhythmias, are of immediate interest to the clinical management of our ageing population [1-4]. In particular, the prevalence of *ventricular arrhythmias* is age-related and has the potential to cause sudden cardiac death (SCD). Indeed the incidence of SCD has been shown to progressively increase with age. SCD is clinically significant as it accounts for ~4 to 5 million deaths per year worldwide. Strategies to address aged related myocardial abnormalities include cardiac stem cell therapy. However, the development of this therapeutic option is limited by our understanding of cardiac stem cell ageing and the effect the ageing process has on cardiac stem cell electrical and molecular properties. Failure for newly implanted cardiac stem cell to electronically and molecularly couple with native cardiac myocytes can alter their activation and propagation activity leading to fatal cardiac arrhythmia. Here we will aim to explore for the effects of ageing on cardiac stem cell electrophysiological properties and correlate these with molecular findings. We will use human ventricular and assess feature of ageing for their (1) electrophysiological properties and for their (2) molecular properties encompassing. We hope to emerge with a detailed clarification of the electrophysiological and molecular features of aged stem cell and in turn develop interventional strategies that will target these effects when developing stem cell therapy.

References: (1) Ahmad S, et al. Reduced cardiomyocyte Na(+) current in the age-dependent murine Pgc-1β(-/-) model of ventricular arrhythmia. J Cell Physiol. 2018 Aug 26. **(2)** Valli H, et al. Age-dependent atrial arrhythmic phenotype secondary to mitochondrial dysfunction in Pgc-1β deficient murine hearts. Mech Ageing Dev. 2017 Oct;167:30-45. **(3)** Ahmad S, et al. Effects of ageing on pro-arrhythmic ventricular phenotypes in incrementally paced murine Pgc-1β (-/-) hearts. Pflugers Arch. 2017 Dec;469(12):1579-1590.

Training/Skills that will be acquired by the student: electrophysiology – microelectrode technique, optical imaging, gene expression, western blot, tissue culture.

Skills/qualifications/interests expected of potential student: computational modelling

Supervisor (s): Dr Kamalan Jeevaratnam (FHMS, Surrey); Dr Prashant Ruchaya (FHMS, Surrey) and Prof Ming Lei (Pharmacology, University of Oxford)

Department(s): Preclinical Veterinary Sciences

C7 Characterizing a novel crosstalk between ER stress and DNA repair in cancer cells.

Abstract

Alkylating agents damage DNA and proteins and are widely used in cancer chemotherapy. Cellular responses to alkylation-induced DNA damage have been well studied, however, knowledge of how cells deal with alkylated proteins, and their effects in alkylating therapy toxicity, is still sparse. Our lab pioneered work characterizing the DNA repair enzyme for alkylation DNA damage, known as alkyladenine DNA glycosylase (AAG)[1–4]. Surprisingly, we recently found that AAG coordinates not only DNA repair but also other cellular stress mechanisms associated with protein damage or misfolding. Combining transcriptomics, bioinformatics, molecular and cellular biology, and using cancer cell lines in addition to the genetically engineered mouse models mentioned above, we showed that AAG is required for the activation of the unfolded protein response (UPR) in the endoplasmic reticulum (ER) in response to alkylation. Our work, therefore, characterizes a novel and hitherto unknown role for this DNA repair enzyme in coordinating alkylation-induced ER stress.

This PhD studentship aims at characterizing this novel function for AAG, identifying how these stress pathways "talk" to each other, and establishing whether AAG co-operates with other proteins in the process. This project will provide state of the art training in proteomics, molecular and cellular biology and the use of genetic models to the PhD candidate. Several pharmacological compounds targeting DNA damage and protein stress response pathways are presently in clinical trials or already in clinical use, so this research has the clear potential to rapidly inform and influence oncology clinical practice.

References:

1. Meira, L. B. *et al.* Repair of endogenous DNA base lesions modulate lifespan in mice. *DNA Repair (Amst).* **21,** 78–86 (2014).
2. Meira, L. B. *et al.* DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. *J. Clin. Invest.* **118,** 2516–25 (2008).
3. Calvo, J. A. *et al.* Aag DNA Glycosylase Promotes Alkylation-Induced Tissue Damage Mediated by Parp1. *PLoS Genet.* **9,** (2013).
4. Meira, L. B. *et al.* Aag-initiated base excision repair drives alkylation-induced retinal degeneration in mice. *Proc. Natl. Acad. Sci. U. S. A.* **106,** 888–93 (2009).

Supervisor (s) and brief biography: Lisiane B. Meira, PhD, Lecturer in DNA Damage and Ageing
Department(s): Department of Clinical and Experimental Medicine

C8 A systematic identification and *in-silico* evaluation of genetic variants associated with vitamin-remedial enzyme activity in humans

Abstract

All B, C, and K vitamins serve as cofactors – helper molecules – to facilitate key enzymatic reactions and determine the activities of hundreds of enzymes. Importantly, one-third of single nucleotide variants (SNV) in gene encoding these enzymes result in the corresponding enzyme having decreased binding affinity for a cofactor resulting in a lower rate of reaction. Previous work into rare, inborn metabolic diseases has shown that "phenotypes" of some mutations in vitamin-dependent enzymes can be suppressed by supplementation of the cognate vitamin, which restores function of the defective enzyme[1]. We hypothesise that such variants – which we refer to as "remedial enzyme variants" might influence human health in a way that could be addressed by elevated vitamin intake! For this PhD project, we will utilise large-scale genetic and clinical/phenotypic data from 2 large UK flagship programs, namely the UK Biobank (www.ukbiobank.ac.uk) and the Genomics England (www.genomicsengland.co.uk) 100,000 Genomes Project to undertake a systematic evaluation of this hypothesis. Our principle focus in this program of work will be to:

(1) Create a catalogue of SNVS, micronutrient-remedial enzymes, cofactor responsive disorders through univariate/multivariate statistical analyses of gene-nutrient interactions; (2) Pathway analysis to unravel aetiological link between cofactor, SNV, and disease; (3)Provide guidelines for "rational" experimental studies aimed to maintain metabolic homeostasis and redress nutritionally-relevant pathways associated with cellular and sub-cellular dysfunction to lower chronic disease risk – i.e. molecular individuality.

Some examples of general questions that will be used to guide further analyses are: Does the prevalence of functional impact correlate with genes identified as risk factors? Are there simple quantitative rules regarding number and severity of dysfunctional alleles? What is the distribution of remedial alleles and is there evidence for nutritional protection by this mechanism?

A major strength of this PhD project proposal, and what distinguishes it from others, is:

(1) As full members of both initiatives we have full access and expertise in handling and analysing this vast resource of genomic and phenomic data; (2) We have an established multidisciplinary team – composed of investigators from University Surrey, Imperial College London, King's College London – to integrate/align expertise in nutritional studies, genomics, analytical biochemistry, and medicine toward the "key" nutritional challenge as described above; (3) Our expertise in both "*in-silico*" and "wet-lab" to assess functionality for some variants as well as determine which alleles may respond to vitamin therapy; and finally, (4) the chance for the student to engage and interact with other researchers currently working on these datasets through attending events and seminars

This has not been undertaken at this scale.

References:

[1] The prevalence of folate-remedial MTHFR enzyme variants in humans. Proc Natl Acad Sci USA. 2008 Jun 10;105(23):8055-60.

[2] Unravelling the basis of variability in cobalamin levels in the general population. Br J Nutr. 2013 Nov 14;110(9):1672-9.

[3] Common genetic loci influencing plasma homocysteine concentrations and their effect on risk of coronary artery disease. Am J Clin Nutr. 2013 Sep;98(3):668-76.

[4] Identification of an imprinted master trans regulator at the KLF14 locus related to multiple metabolic phenotypes. Nat Genet. 2011 Jun;43(6):561-4.
[5] Interaction between plasma homocysteine and the MTHFR c.677C > T polymorphism is associated with site-specific changes in DNA methylation in humans. FASEB J. 2018 Aug 6:fj201800400R
[6] Vitamin D supplement use and associated demographic, dietary and lifestyle factors in 8024 South Asians aged 40-69 years: analysis of the UK Biobank cohort. Public Health Nutr. 2018 Oct;21(14):2678-2688.
[7] Genetic polymorphisms that affect selenium status and response to selenium supplementation in United Kingdom pregnant women. Am J Clin Nutr. 2016 Jan;103(1):100-6.

Training/Skills that will be acquired by the student:
It will be essential that the student completes all 3 modules of the online SysMIC course. Furthermore, the student will also attend the following national courses during years 1-2:
(1) Specific modules of the Human Molecular Genetics MSc course (co-ordinator Dr Toby Andrew, 3rd supervisor) at Imperial College: Basic genetics, Statistical genetics, Bioinformatics;
(2) International Course in Nutritional Epidemiology (Imperial College).
(3) The Leena Peltonen Summer School of Human Genomics: Wellcome Trust Genome Campus, which provides intensive training in the genetic analysis of multifactorial traits.
The student will attend the annual nutritional society meetings as well as two international conferences to present her work in years 3-4 of her studies, including:
(1) Keystone Symposia: Nutrition, Epigenetics and Human Disease (2016-17).
(2) Wellcome Trust: Epigenomics of Common Diseases (2016-17).
Skills/qualifications/interests expected of potential student: A general interest in either or Nutrition, Human Genetics and clinical medicine is needed. The project is a computer-based study and so the student will have to be happy to not be in a laboratory and working in front of a computer. Competency in human genetics, statistics and computer coding (Unix or R) are highly desirable. Above all a desire to apply statistical genomics tools to unravel the relationship between Nutrition/food and human health with a clinical setting.
Supervisor (s) and brief biography: Kourosh R Ahmadi (PhD), Martin Whyte (MBBS, PhD), Toby Andrew (PhD). KRA is a population Geneticist and his research portfolio focuses on developing precision nutrition-based risk-management strategies for common “ageing” diseases. MBW is a clinical senior lecturer in metabolic medicine NHS consultant Diabetologist (KCH). He has extensive experience of detailed clinical/metabolic studies. TA is a lecturer in Geneticist and his research focuses the role of mitochondria in metabolic disease using bioinformatics and statistical tools.
Department(s): Department of Nutrition (UoS), Department of Clinical & Experimental Medicine (UoS), Department of Medicine (Imperial College, London)

C9 Co-expression of circadian and ultradian rhythms in metabolism

Abstract
Biological rhythms are a highly conserved biological phenomenon seen across all animal species. For instance, behavioural and physiological processes such as sleep-wake regulation, gene expression, and metabolism cycle through peaks and troughs once, or several times, a day. It is now clear that 24-hour (circadian) rhythms are driven by cellular clocks (a discovery that was awarded the Nobel Prize in Physiology or Medicine in 2017), and that disturbing these rhythms can have negative metabolic consequences such as obesity and diabetes.
It is however mostly overlooked that the 24-hour rhythms in metabolic physiology are often co-expressed with rapid – ultradian – rhythms in the hourly range in the very same biological processes. To date, it is unclear what the scope and biological function of these ultradian rhythms are, or what drives and synchronises them. We recently developed a novel mathematical approach designed to specifically isolate rapid ultradian rhythms in gene expression, and found that ultradian gene expression is a true biological rhythm that persists in cell culture. We exposed that ultradian gene expression was primarily involved in cellular metabolism, and the cell cycle, and we have since developed a cell culture model for ultradian rhythmicity.
The aim of this project is to further develop this model, and for the first time describe how these rhythms are synchronised to timing cues such as temperature, the cell cycle phase, and the co-expressed circadian clock. You will develop a real-time bioluminescence reporter construct for ultradian rhythms in gene expression for use in several cell types (fibroblast, liver cells, etc). Using this high-resolution model, you will investigate the properties of cellular ultradian rhythms in gene expression (qPCR) and consumption of different energy sources. You will next use pharmacological and culturing interventions to define the timing cues that synchronise ultradian rhythms in this model. Finally, you will use CRISPR technology to perturb the 24-hour circadian clock, and describe ultradian rhythms in the absence of a circadian clock.
References:
Van der Veen, D.R. & Gerkema, M.P. (2016) Unmasking ultradian rhythms in gene expression. FASEB J.
Van der Veen, D.R. et al (2006) Impact of behavior on central and peripheral circadian clocks in the common vole Microtus arvalis, a mammal with ultradian rhythms. Proc Natl Acad Sci USA
Van der Veen D.R. et al (2017) Flexible clock systems: adjusting the temporal programme. Philos Trans R Soc Lond B Biol Sci.
Supervisor(s) and brief biography: Dr Daan R van der Veen
Dr Van der Veen is a Lecturer in sleep and Chronobiology, and his research focusses on the contribution of individual biological clocks such as in the liver, heart, and brain to overall biological timing of physiology and behaviour. Dr Van der Veen takes an interdisciplinary approach generating molecular and –omics datasets of pre-clinical and cell culture models, and combining this with tailored statistical and mathematical approaches, to ask the questions on the molecular physiological properties of biological rhythmicty, and what their significance is to a healthy, flexible timing system.
Department(s): School of Bioscience and Medicine, Faculty of Health and Medical Sciences

C10 Translational control of autophagy – a vital induction mechanism?

Abstract
The Objectives of this PhD research project are to: 1) define the mechanism controlling expression of autophagy proteins whose abundance are regulated at the level of translation, particularly in the Integrated Stress Response, and 2) determine the dependence of homeostatic and pathogenic selective autophagy on the eIF2α signalling pathway.
The candidate will receive research training in Dr Rachel Simmonds' Wellcome Trust funded research group at the University of Surrey. You will be based in the School of Biosciences and Medicine in the Faculty of Health and Medical Sciences, at our beautiful Stag Hill Campus. Dr Simmonds has a strong track record of successful research mentorship.
Selective autophagy is an important cellular mechanism that plays a vital role in a range of functions from the removal of misfolded proteins, aggregates or damaged organelles to the killing of intracellular bacteria. In work leading up to this project, we have discovered that overloading the cells with mislocalised proteins, due to the action of mycolactone, results in translational reprogramming of the cell and autophagy. We have identified autophagy-related proteins that are upregulated at the translational level during the Integrated Stress Response (ISR). Although many experimental inducers of autophagy affect this pathway, which is intimately linked to translation, the phenomena of translational control in autophagy is completely unaddressed in the field. In this project you will explore the mechanistic link between the autophagy, translation and the ISR.
Methods: This project will provide opportunities to develop a wide range of skills. You will receive training in the cutting edge molecular and cell biology techniques you will use in this project. This includes cell signalling, imaging, molecular biology, and analysis of "translatomics" data sets.
References
Ogbechi *et al.* Inhibition of Sec61-dependent translocation by mycolactone uncouples the integrated stress response from ER stress, driving cytotoxicity via translational activation of AFT4. Cell Death Dis 2018: 9; 397
Skills/qualifications/interests expected of potential student: Strong Molecular Biology background

Supervisor (s) and brief biography: Dr Rachel Simmonds is Senior Lecturer in Immunopathogenesis. She trained and works as a eukaryotic molecular biologist (BSc University of Manchester, PhD Imperial College London). She has made significant contributions to the understanding of different infectious and non-infectious human diseases. Rachel was appointed to the University of Surrey in 2011 after receiving her first award from the Wellcome Trust. The thriving group focusses on a potent protein translocation inhibitor and exotoxin, mycolactone, whose mechanism of action was discovered in her lab. https://www.surrey.ac.uk/people/rachel-simmonds
Department(s): School of Bioscience and Medicine

C11 Engineering mammalian cells for complex tasks accounting for the interplay between synthetic genetic circuits and the host used for expression

Abstract
One of the goals of Synthetic Biology is the design of genetic circuits endowing cells with functions that are predictable. A challenge limiting the implementation of this goal is the context dependence of the genetic circuits used to engineer cells for a particular function. In particular, exogenous genes required for applications have to share with the host the transcriptional and translational machinery required for expression. This has a double impact: on one hand the physiology of the host is affected (loss of fitness) and, on the other hand, the performance of the synthetic genetic circuit differs from what is expected sometimes leading to complete failure. This interplay between exogenous DNA encoding for genetic circuits and the host required for gene expression has been widely characterised in bacterial cells but has not been explored in more complex cellular systems like mammalian cells, in which the resources available for gene expression are severely limited and their allocation compromises cell survival. In this PhD project we will focus on the quantitative analysis of resource allocation in mammalian cells, studying the impact of synthetic circuits of increasing complexity. We will adapt for this purpose experimental (molecular biology, CRISPR, flow cytometry) and computational (mathematical modelling with ODEs) methods developed in microbial organisms by Dr. Jimenez and study their impact on mammalian cells with the aim of improving strains developed by Prof. McVey (cell culturing, cell biology). As a result of this interdisciplinary project we will obtain better design strategies of circuits expressed in mammalian cells with potential applications in stem-cell engineering, therapeutic recombinant protein production and gene therapy.
References:

- Darlington *et al.*, (2018) Nature Communications. 9:695
- Qian *et al.*, (2017) ACS Synthetic Biology. 6(7):1263-1272
- Gyorgy *et al.*, (2015) Biophysical Journal. 109(3):639-646
- Chen *et al.*, (2017) Frontiers in Immunology. 9:1517
- Shestopal *et al.*, (2017) Journal of Thrombosis and Haemostasis. 15(4):709-720

Training/Skills that will be acquired by the student: Molecular biology, cell biology, cell culturing, CRISPR, flow cytometry, microscopy imaging, RNAseq.
Skills/qualifications/interests expected of potential student: An interest in quantitative aspects of biology is a plus together with previous experience in molecular biology and working with mammalian cell lines.

Supervisor (s) and brief biography: Dr. Jose Jimenez and Prof. John McVey
Jose Jimenez is a Senior Lecturer that established his lab at Surrey in 2014. He has a strong research agenda in diverse topics ranging from health to environmental Synthetic Biology and his work is currently sponsored by BBSRC, NERC, the Royal Society, the Leverhulme Foundation and the H2020 programme of the European Union. After earned his Ph.D. in Biochemistry and Molecular Biology in Spain and the conducted postdoctoral stays at Harvard University and MIT (USA).
John McVey John McVey is Professor of Cardiovascular Biology at the University of Surrey and holds an Honorary Professorship at University College London (UCL). His research focuses on the regulation of blood coagulation and the role that coagulation factors play in normal physiology and

in the pathophysiology of disease. Professor McVey has published in excess of 120 research articles, reviews, and books. He has received major grant funding from the MRC, Wellcome Trust, BBSRC and BHF. He is a named inventor on 3 patents. He is a fellow of the Royal College of Pathologists.
Department(s): Microbial Sciences and Biochemistry

D. Neuroscience and Psychology

D1 Dynamic modulation of brain states using non-invasive brain stimulation

Abstract

In order to support cognitive functions, the brain must coordinate the interactions among large-scale networks that cooperate and compete to allow for efficient transitions between brain states. Understanding how these operate, giving rise to different behaviours is one of the greatest challenges facing modern neuroscience. The overarching aim of this project is to develop a framework capable of shaping the interactions between brain networks. In order to do this, we will combine transcranial alternating current stimulation (tACS) with a novel approach, neuroadaptive Bayesian optimization. TACS is a promising tool to modulate brain function. The oscillatory electrical activity imposed by tACS has been shown to result in neural modulations that spread along brain networks. However, there are two main limitations to the application of tACS to modulate brain function: 1) the brain networks targeted by stimulation cannot be verified in the absence of brain imaging; 2) the stimulation parameters vary across individuals, due to a multitude of variables, such as age, sex and genetic factors. Thus, identifying the optimal stimulation protocol that drives a particular brain state in a given individual is like finding a needle in a haystack. To address these fundamental challenges, we propose to use neuroadaptive Bayesian optimization, which uses a close-loop search combining real-time fMRI with machine learning. This approach conducts an automatic and intelligent search across the multitude of tACS parameters in order to identify those that optimally elicit a particular target state. This framework has translational potential, as several psychiatric and neurological conditions are associated with impaired function of large-scale brain networks. The results of this project can lead to the development of therapeutic interventions that harness the potential of brain stimulation.

References:

Lorenz R, Violante IR, Monti RP, Montana G, Hampshire A, Leech R. Dissociating frontoparietal brain networks with neuroadaptive Bayesian optimization. Nature Communications (2018) 26;9(1):1227. doi: 10.1038/s41467-018-03657-3.

Violante IR, Li LM, Carmichael DW, Lorenz R, Leech R, Hampshire A, Rothwell JC, Sharp DJ. Externally induced frontoparietal synchronization modulates network dynamics and enhances working memory performance. eLife (2017), Mar 14;6. pii: e22001. doi: 10.7554/eLife.22001.

Supervisor (s) and brief biography: Dr. Ines Violante

Ines is a Lecturer in Psychological Neuroscience at the University of Surrey. She has recently been awarded a New Investigator Award (BBSRC) to establish an interdisciplinary line of research on cognitive neuroscience focusing on brain networks, neuromodulation, and the development of tools for translational research methods for clinical applications. Her research combines functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to understand how brain stimulation (TMS, tACS, tDCS) can be used to modulate brain dynamics and behavioural performance. Ines is interested in how brain oscillations mediate long-range connectivity and particularly how neurostimulation can be used to improve network communication following neurological and psychiatric disorders.

External Supervisor: Prof. Rob Leech – King's College London

Rob is Professor of Neuroimaging Analytics at King's College London. His lab pioneered Bayesian optimization combined with real-time fMRI and applied it to research questions in cognitive neuroscience. His group is at the forefront of the development of Bayesian optimization approaches for neuroimaging, as well as the improvement of computational models of cognitive function. H-index: 38, citations: 6k.

Department(s): School of Psychology, FHMS

D2 A precise characterisation of the Down syndrome visuo-spatial profile and the impact of this on number and mathematics ability.

Abstract

Down syndrome (DS) is a genetic disorder with a prevalence of ~1 per 1000 live births (de Graaf et al., 2011). Individuals with DS have an IQ of ~ 50 to 70, but this masks an uneven cognitive profile characterised by relatively more severe impairment in verbal ability than visuo-spatial ability. While there is a substantial literature on the impaired verbal domain in DS, little is known about the visuo-spatial domain in DS. This is despite the knowledge that visuo-spatial skills are vital to everyday living. For example, being able to remember where things are kept in your room, the ability to pack a bag, and the ability to learn your way around a new school or workplace (Farran et al., 2015). Visuo-spatial ability is also a strong contributor to mathematics and number development, for example using number lines and understanding magnitude (e.g. Uttal, Miller & Newcombe, 2013; Gilligan, Flouri & Farran, 2017). A recent exhaustive review suggested an uneven profile of visuo-spatial abilities in DS (Yang et al., 2014). However, the majority of the 49 papers reviewed concerned memory measures. The precise level of ability for other aspects of visuo-spatial cognition could not be determined. This demonstrates a crucial need to better understand the visuo-spatial cognitive profile in DS. In this PhD studentship, the student will first fully characterise the visuo-spatial cognitive profile in DS for the first time (Phase 1). The second aim of this PhD studentship (Phase 2) is to design learning approaches to facilitate learning in the domain of number and mathematics which optimise on the strengths in the DS visuo-spatial cognitive profile.

References:

Gilligan, K., Flouri, E., **Farran, E.K.** (2017). The contribution of spatial ability to mathematics achievement in middle childhood. *Journal of Experimental Child Psychology*. *163, 107-125*. doi.org/10.1016/j.jecp.2017.04.016

Farran, E.K. Purser, H.R.M., Courbois, Y., Ballé, M. Sockeel, P., Mellier, D, Blades, M. (2015). Route knowledge and configural knowledge in typical and atypical development: a comparison of sparse and rich environments. *Journal of Neurodevelopmental Disorders, 7:37*. doi: 10.1186/s11689-015-9133-6

Uttal, D. H., Miller, D. I., & Newcombe, N. S. (2013). Exploring and enhancing spatial thinking: Links to achievement in science, technology, engineering, and mathematics? *Current Directions in Psychological Science, 22*(5), 367-373.

Yang, Y., Conners, F. A., & Merrill, E. C. (2014). Visuo-spatial ability in individuals with Down syndrome: Is it really a strength? *Research in Developmental Disabilities, 35*(7), 1473-1500.

Supervisor (s) and brief biography:

Prof. Emily Farran: My research relates to cognitive development in neurodevelopmental disorders (Williams syndrome, Down syndrome, Developmental Coordination Disorder, Attention Deficit Hyperactivity Disorder) and in typical development, with a specific emphasis on spatial cognition.

Dr. Katie Gilligan: My research focuses on the interrelated development of spatial and mathematical thinking. I am particularly interested in novel methods of training spatial abilities, and exploring transfer of spatial training gains to other untrained domains (e.g., mathematics, science).

Department(s): School of Psychology

D3 Understanding how altered translation contributes to neurodegenerative diseases using novel stem cell models

Abstract

Neurodegenerative disorders (NDs) affecting the ageing population are characterized by the loss of specific cells. In response to stress, such as neurodegeneration, cells can pause protein synthesis, or translation, by storing messenger RNAs away in cellular compartments called stress granules. This defense mechanism allows cells to survive by limiting the use of energy, pausing general translation while allowing the specialized translation program essential to stress recovery. If prolonged, this stress can lead to cell toxicity and death. Neurons are highly specialized cells reliant on accurate control of translation to maintain their unique functions throughout the lifespan. Not surprisingly the dysregulation of the translation pathway is central to the pathogenesis of several NDs. Furthermore, restoring translation activity in model systems can decrease the severity of disease. Therefore the regulation of translation is a promising therapeutic target for treating treatment of NDs. To understand of how translation regulation affects the loss of neuronal functions, we will use novel genetically engineered isogenic human stem cell lines to generate neuronal populations representative of Alzheimer's disease (AD) and Parkinson's disease (PD) which cover >70% of NDs patients. In control and disease cells, we will 1-measure global translation activity at the single cell level and characterise the presence of stress granules, 2-dissect the stress-specific translation program triggered by the cell and 3-measure the impact of the NDs on the metabolism and phenotype of ageing neurons. This work will provide new leads for the therapeutic restoration of translation in NDs of the ageing population.

References:

In addition to those in CV: mRNA circularization by METTL3-eIF3h enhances translation and promotes oncogenesis. Choe J et al. *Nature* 2018. 561(7724):556-560. Disturbances of sleep quality, timing and structure and their relationship with other neuropsychiatric symptoms in Alzheimer's disease and schizophrenia: insights from studies in patient populations and animal models. Winsky-Sommerer et al, *Neurosci Biobehav Rev* 2018 S0149-7634(17)30879-5.

Training/Skills that will be acquired by the student: RNA biology, immunofluorescence microscopy, cell culture (stem cells).

Supervisor (s) and brief biography: Dr Nicolas Locker is an expert in RNA biology and diseases; his work has been published in Nature, Nucleic Acids Research, mBio; research in his lab is supported by funding from the Medical Research Council and Biotechnology and Biological Sciences Research Council. **Dr Raphaelle Winsky-Sommerer**'s research focuses the relationship between chronic stress, neurodegeneration and sleep disturbances; her work has been published in Science, Current Biology, Journal of Neuroscience; research in her lab has been supported by funding from the Biotechnology and Biological Sciences Research Council, pharmaceutical industry and philanthropic gift.

Departments: Microbial Sciences / Clinical and Experimental Medicine

D4 Developmental science of children's self-control

Abstract
Levels of self-control during childhood predict success and health in adult life (Moffitt et al., 2011). Subsequently, universal interventions that boost children's self-control may have substantial impact on public health, wealth and safety. However, there is currently very limited evidence supporting specific interventions and more evidence is needed before interventions can be recommended to policymakers. This PhD will investigate both the early precursors of childhood self-control (e.g., parenting, friendships, childcare) to identify intervention targets and test the efficacy of interventions targeting young children's self-control (e.g., martial arts training).

References:

Lakes, K. D., & Hoyt, W. T. (2004). Promoting self-regulation through school-based martial arts training. *Journal of Applied Developmental Psychology*, *25*(3), 283-302.

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., ... & Sears, M. R. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences*, *108*(7), 2693-2698.

Ng-Knight T, Shelton K, Frederickson N, McManus I, Rice F (2017) Maternal depressive symptoms and adolescent academic attainment: testing pathways via parenting and self-control, Journal of Adolescence 62 pp. 61-6

Ng-Knight T, Shelton K, Riglin L, McManus I, Frederickson N, Rice F (2016) A longitudinal study of self-control at the transition to secondary school: Considering the role of pubertal status and parenting, Journal of Adolescence 50 pp. 44-55

Ng-Knight T, Schoon I (2016) Disentangling the Influence of Socioeconomic Risks on Children's Early Self-Control, Journal of Personality 85 (6) pp. 793-806

Training/Skills that will be acquired by the student:
The PhD student will develop skills analysing complex longitudinal data (such as the UK's world renowned cohort studies) and running experimental intervention studies with school-aged children.

Skills/qualifications/interests expected of potential student:
Interests in developmental, educational and/or personality psychology are essential.

Supervisor (s) and brief biography: Dr Terry Ng-Knight and Professor Jane Ogden, School of Psychology.

Dr Ng-Knight is a Lecturer in Personality & Individual Differences. He has expertise in advanced quantitative methods and experience running longitudinal studies. He has a track record of publishing his work on the development of self-control in top international journals.

Jane Ogden is a Professor of Health Psychology. Her research explores aspects of health including obesity and eating behaviour, communication in the consultation, and women's health issues. She has a distinguished track record in the field, having established a successful course in health psychology and taught at several leading institutions. Jane is the author of eight books and has published 190 research papers.

Department(s): Psychological Sciences

D5 International Social Perceptions of Energy Security (iSpies)

Abstract

Energy security (ES) is a complex phenomenon. While it can be simply construed as ensuring the uninterrupted availability of energy at an affordable price, modern definitions have evolved to become more inclusive; recognising not only the quantifiable, market-centric roots of ES—governed by considerations of energy supply and price—but also more qualitative considerations such as governance and social acceptability [1].

The incorporation of social acceptability into the definition of energy security, in particular, is important bearing in mind the influence that socio-political, market and community stakeholders (including general publics) exert on energy and environmental policy and decision-making [8-10]. Social scientific understanding of ES perceptions remains in its infancy, however, there is emerging evidence of how attitudes towards the issue are embedded within and shaped by the specific socio-economic and cultural systems of a given country [2, 3].

iSpies is designed to provide in-depth insight into the psychological factors shaping perceptions of ES among different stakeholder groups from a number of countries. The project will conduct a state-of-the-art, internationally-focused, systematic review of social perceptions of ES before designing and running a series of studies designed to provide a comparative, theoretically-informed analysis of ES perceptions in a number of countries.

The types of studies that could be conducted in this space are open to discussion; however, they would likely include: (a) large-scale quantitative surveys of lay-public perceptions of ES: and (b) qualitative interviews with select representatives of key stakeholder groups. While the primary focus of the research will be on assessing energy security in relation to electric power generation, supply and use; broader issues of ES relating to other sectors (e.g. transportation, heating) could also be considered. Dr Jones has research links to a number of countries (Canada, Greece, Turkey, Germany) that could be accessed in relation to this project.

References (underlining those generated by the Surrey lab and/or supervisor:

[1] J. Knox-Hayes, M.A. Brown, B.K. Sovacool, Y. Wang, Understanding attitudes toward energy security: results of a cross-national survey, Glob. Environ. Change 23 (2013) 609–622.

[2] B.K. Sovacool, Differing cultures of energy security: an international comparison of public perceptions, Renew. Sustain. Energy Rev. 55 (2016) 811–822.

[3] Jones, C. R. Jones, D. Kaklamanou, L. Lazuras, L. Public perceptions of energy security in Greece and Turkey: Exploring the relevance of pro-environmental and pro-cultural orientations. *Energy Research & Social Science 28* (2017) 17-28.

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Dr. Jones is a social and environmental psychologist with a background in the theory and principles of attitude formation and change. His research interests centre on: (a) understanding public perceptions of technology, particularly energy supply and demand-side technologies; and (b) understanding the antecedents and barriers to pro-environmental behaviour in the context of prominent contemporary environmental risks (e.g. climate change).

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