Theme 3
Physiological Medicine

2021/2022

Theme 3 Physiological Medicine

This theme explores synergies between organ-based physiology disciplines and has a translational research emphasis, focusing on cardiovascular and respiratory disease, foetal and maternal health, and diabetes/obesity. These areas are the core of our "Clinical Medicine" research area, and link strongly into the Guy's and St. Thomas' Biomedical Research Centre. Links to other foci of scientific excellence (e.g. in vivo imaging, bioinformatics, computational modelling) underpin an interdisciplinary ethos.

Lead: Professor Cathy Shanahan

When choosing a project from this catalogue in the funding section of the online application form please enter: MRC DTP2021_Theme 3

Application Deadline: 29th of November 2020

Shortlisted candidates will be contacted in mid-January.

Interviews: 27th and 28th January 2021

The 2021/22 studentships will commence in September 2021.

For further Information or queries relating to the application process please contact mrc-dtp@kcl.ac.uk

Projects listed in this catalogue are subject to amendments, candidates invited to interview will have the opportunity to discuss projects in further detail.

Contents

1.3 Gestational diabetes and depression: A role for islet serotonin

Co-Supervisor 1: Dr James Bowe
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Project description:

During pregnancy insulin resistance increases and maternal islets of Langerhans adapt by increasing both insulin secretory response and β-cell mass. Gestational diabetes (GDM) occurs when the islets are unable to adapt sufficiently. The signals underlying this islet adaptation are poorly understood, however recent studies show islet serotonin to be a key local mediator. Normally β-cell serotonin expression is negligible, but levels increase during pregnancy due to placental signals such as lactogens and kisspeptin. Reduced islet serotonin signalling during pregnancy leads to impaired glucose tolerance and GDM.

GDM is also associated with depression, though the mechanism is unclear. The most common therapeutics for treatment of depression are serotonin reuptake inhibitors (SSRIs), which increase availability of endogenous serotonin. SSRIs have also been shown to stimulate islet function and are likely to influence the action of endogenous islet serotonin during pregnancy.

This project will use a combination of in vivo and primary tissue studies to address two aims:

- How does is endogenous β-cell serotonin involved in the islet adaptation to pregnancy?
- Do SSRIs improve the islet adaptation to pregnancy?

Initially the student will use tissues from mouse models to assess the effects of serotonin on β-cells. Techniques will include RNAscope, immunohistochemistry and hormone assays. From year 2 onwards the student will use in vivo models to examine the effects of SSRIs on glucose homeostasis in pregnant animals and models of depression. Subsequent studies may examine the longer term effects of SSRIs in pregnancy on the metabolic health of both mother and offspring.

Representative publications:

- Bowe, J. E., Hill, T. G., Hunt, K. F., Smith, L. I. F., Simpson, S. J. S., Amiel, S. A., Jones, P. M. (2019) A role for placental kisspeptin in β cell adaptation to pregnancy. JCI Insight. 4(20); DOI:10.1172/jci.insight.124540
- Taylor, P. D., Matthews, P. A., Khan, I. Y., Rees, D., Itani, N. & Poston, L. (2018) Generation of Maternal Obesity Models in Studies of Developmental Programming in Rodents. Methods in molecular biology 1735; 167-199

2.3 Assessing cardiorespiratory pathology in chronic lung disease using a novel medical technology

Co-Supervisor 1: Dr Richard Bruce
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Co-Supervisor 2: Dr Caroline Jolley
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Project description:

The assessment of many respiratory diseases is largely dependent on traditional lung function tests such as spirometry. However, these tests are very blunt tools; they are often insensitive to early signs of disease and are poor predictors of long-term outcomes. They also require active patient involvement, which is difficult/impossible in many settings such as intensive care. The inspired sinewave technique (IST) is a novel medical device which measures cardiorespiratory function using inhaled tracer gases, and has been designed to meet these challenges. The IST is engineered at the University of Oxford and is being clinically tested at Kings College London/Hospital as part of a collaborative NIHR grant.

Over 3 years we aim to further validate the technology in healthy participants, and compare its assessment of different lung diseases with traditional pulmonary function tests and chest CT. A PhD student would have an excellent opportunity to develop numerous skills including full lung function testing, the assessment of neural respiratory drive via parasternal electromyography, computer analysis of chest CT scans, data/statistical analysis, and the performance and technical development of the IST. The student can also be introduced to skills in the mathematical modelling of physiological systems and the engineering of new hardware and software.

Year 1: Gain proficiency in laboratory skills, and perform further validation tests with the IST and healthy participants.
Year 1/2: Test the IST with respiratory outpatients and those at risk of respiratory disease (smokers)
Year 3: Re-test a sample of patients (+12 months). Pilot testing in intensive care.

Representative publications:

- Bruce R. M, Crockett, D, Morgan, A, Tran, M, Formenti, F, Phan, P & Farmery, A (2019), 'Cardiac output monitoring in a porcine model using the inspired sinewave technique: a proof-of-concept study', British Journal of Anaesthesia.
- Jolley CJ, Luo YM, Steier J, Rafferty GF, Polkey MI, Moxham J. Neural respiratory drive and breathlessness in COPD. European Respiratory Journal. Feb;45(2):355-364 (2015)

3.3 Combining electronic health record and translational biological approaches for drug repurposing for cancer therapy

Co-Supervisor 1: Dr Elizabeth Davies
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http://goo.gl/NsFAkV

Project description:

This multi-disciplinary research aims to provide an evidence base for the augmentation of drugs available for cancer therapy. The drugs to be evaluated are termed membrane potential regulating compounds (MPRCs) and are in current clinical use to treat diseases other than cancer. Some MPRCs are known in the epidemiology literature to have a cancer protective effect. MPRCs were discovered in the Ahmed laboratory as novel inhibitors of the Wnt signalling pathway, a key carcinogenic signalling network. The objective will be to 'repurpose' MPRCs for prostate cancer therapy.

Hypothesis: MPRCs have a cancer protective effect and hence reduce the incidence cancer progression in patients prescribed with these drugs and dampening of key carcinogenic pathways by MPRCs could be an anticarcinogenic mechanism in patients prescribed these drugs.

Aims and techniques:

1. Electronic health record (EHR) interrogation: to assess and phenotype which of the initial list of 50 MPRCs are associated with reduced incidence and/or progression of prostate cancer.
2. Target validation: of 10 most effective MPRCs from EHR analysis that reduce incidence and inhibit cancer progression in human tissue samples ± cancer ± MPRCs. A multiomic approach using targeted gene sequencing, single molecule RNA and quantitative, large scale, multilabel protein expression analysis for key carcinogenic pathways will be employed.
3. Data integration: of large scale EHR and biological data to produce a data repository for use in prostate cancer research.

Both EHR analysis and biological validation techniques are established in the Davies and Ahmed laboratories.

Representative publications:

- **Davies EA**, Coupland V, Dixon S, Mokbel K, Jack R. Comparing the case mix and survival of women receiving breast cancer care form one London provider with other London women with breast cancer: pilot data exchange and analyses BMC Cancer 2016;16,421 doi:10.1186/s12885-016-2439-2

- Ashmore, J, Olsen, H, Sorensen, N, Thrasivoulou, C and **Ahmed, A**. Wnts control membrane potential in mammalian cancer cells. J Physiol, 597: 5899-5914, 2019.

4.3 Strong bones, strong muscle? - the role of oestrogen in muscle mass and function

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Project description:

Good musculoskeletal health is critical for healthy ageing but beset by multiple threats. Low muscle mass and poor muscle function (i.e., sarcopenia) cause disability, poor quality of life, and falls; and osteoporosis, the almost inevitable accompaniment of sarcopenia, causes fracture. There is a bidirectional relationship between muscle and bone. Whilst the deleterious bone effects of oestrogen deficiency are extremely well-known (most evident in women, because of menopause, but also seen in men) the effect on muscle, and any contribution to sarcopenia, are less clear. The aims of this project are to assess the role of oestrogen in muscle, through population studies and in vitro approaches. Specifically:

a) Year 1: Measures of muscle mass (e.g., DXA-assessed lean body mass) and function (e.g., grip strength) will be compared in postmenopausal women, between users and non-users of menopausal hormonal therapy. The large longitudinal cohorts of Twins UK and Framingham studies will allow comparisons between users and non-users; and intra-individual change pre- and post-use. The candidate will develop skills in epidemiology, statistics, and big data management.
b) Years 2 and 3: The effect of oestrogen on cultured myoblasts and myotubes will be determined, assessing cellular proliferation, differentiation, myosin isotype composition, and function (e.g., contractile profiling). Effects on gene expression (e.g., on critical FoxO-1 pathways) will be assessed via RNAseq. The candidate will learn cell culture, histology, functional assessment, RNA extraction, and expression analysis.

Given ageing populations world-wide, the translational potential is huge: the 'holy grail' of an anabolic agent for osteosarcopenia.

Representative publications:

- Zheng HF, Forgetta V, Hsu YH, et al. (**Duncan EL** co-senior author) Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. Nature. 2015;526(7571):112-117. doi:10.1038/nature14878
- Bennett, P., M. Rees, and **M. Gautel**, The Axial Alignment of Titin on the Muscle Thick Filament Supports its Role as a Molecular Ruler. J Mol Biol, 2020. 432(17): p. 4815-4829. PMID: 32619437

5.3 First-in-man arterial oxygen sensing in acute lung injury

Co-Supervisor 1: Dr Federico Formenti
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Project description:

Scientific basis and importance: The Acute Respiratory Distress Syndrome (ARDS) is a condition that affects several patients in the intensive care unit, with ~40% mortality rate. Patients with ARDS require mechanical-ventilator support, yet this respiratory support needs to be individualised, as inappropriate mechanical ventilation can worsen lung injury and result in considerable attributable mortality. Currently, no bedside technology is available to guide real-time personalised mechanical ventilation in ARDS patients.

A prototype fast-responding arterial oxygen sensor, recently validated in animal models, enables the continuous monitoring of respiratory arterial oxygen oscillations, which are exaggerated in lung injury. Monitoring these oscillations at the bedside may provide real-time information on the safest way to deliver mechanical ventilation, aimed at maintaining the oscillations' amplitude within the normal range.

Translational aspects: This project covers the whole span from pre-clinical studies in a pig model (at the University of Uppsala, Sweden) to patient studies at St Thomas' Hospital in London.

Training, techniques and skills: training will be offered across the wide range of multidisciplinary techniques and skills that the candidate will acquire during the project. These include physiological waveform analysis, image analysis (dual-energy computed tomography and electrical impedance tomography), statistics for the biomedical sciences and scientific writing.

Objectives:

1) complete a pre-clinical trial in a pig model of lung injury, where standard-of-care is compared with individualised mechanical ventilation;
2) use pre-clinical trial data to develop algorithms for real-time analysis of arterial oxygen and physiological waveforms;
3) complete a first-in-man observational patient study.

Representative publications:

- Perrotta S, Roberti D, Bencivenga D, Corsetto P, O'Brien KA, Caiazza M, Stampone E, Allison L, Fleck RA, Scianguetta S, Tartaglione I, Robbins PA, Casale M, West JA, Franzini-Armstrong C, Griffin JL, Rizzo AM, Sinisi AA, Murray AJ, Borriello A**, Formenti F**, Della Ragione F. Effects of germline VHL deficiency on growth, metabolism, and mitochondria. NEJM 2020

- Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, **Camporota L**, Slutsky AS: Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012

6.3 Studying the Tie-1 receptor in vascular endothelial cells: potential role as promoter of vascular remodelling/repairin diabetes.

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Project description:

Scientific basis of project: Theangiopoietin (Angpt) system is composed of Angpt1 that mediates Tie2receptorphosphorylation/activation promoting vascular stability and Angpt2 (which competes for the Angpt1/Tie2 binding) blocking the action of Angpt1. Diabetes is associated with an imbalance in the Angpt system (Angpt2>Angpt1) leading to vascular disease. The Tie1receptor, by interacting with Tie2, regulates Tie2 signalling. Tie1 is required for Angpt1/2-mediated Tie2 phosphorylation. Loss of Tie1, seen in diabetes, results in loss of Angpt2-mediatedTie2 receptor phosphorylation.

Hypothesis: Tie1overexpression protects the diabetic vasculature.

Objective and skills: The student will gain an understanding of experimental diabetes through cutting edge in vitro/in vivo techniques and translational medicine through study of human samples.
In the mini-project and year-1, study of vascular morphology/functions in cells and tissues from diabetic mice will determine influence of Angpt1/2 and Tie1/2levels. Techniques include cell culture, DNA cloning and adenoviral vector biology; angiogenesis assays, cell monolayer permeability, confocal microscopy.
In year-2 in the diabetic mouse the matrigel angiogenesis assay and the study of skin blood flow via laser imaging will investigate the role of Tie1 on vascular function.
In year-3 clinical studies (ethics in place) will allow translation of results. We will measure the circulating level of Angpt1/2 and sTie1, product of Tie-1 shedding/degradation, (by ELISA) in non-diabetic controls and patients with type1 diabetes (either susceptible or protected from development of chronic microvascular complications).
The supervisors: a clinical researcher diabetic expert (LG) and a vascular biology basic scientist (SB) have adjacent laboratories and joint funding.

Representative publications:

- Dessapt-Baradez C, Woolf AS, White KE, Pan J, Huang JL, Hayward A, Price KL, Kolatsi-Joannou M, Locatelli M, Diennet M, Webster Z, Smillie SJ, Nair V, Kretzler M, Cohen CD, Long DA, **Gnudi L.** Targeted glomerular angiopoietin-1 therapy for early diabetic kidney disease. JAm Soc Nephrol. 2014, 25(1):33-42.doi: 10.1681/asn.2012121218
- Aubdool AA, Thakore P, Argunhan F, Smillie SJ, Schnelle M, Srivastava S, Alawi KM, Wilde E, Mitchell J, Farrell-Dillon K, Richards DA, Maltese G, Siow RC, Nandi M, Clark JE, Shah AM, Sams A, **Brain SD**. A Novel α-Calcitonin Gene-Related Peptide Analogue Protects Against End-Organ

Damage in Experimental Hypertension, Cardiac Hypertrophy, and Heart Failure. Circulation. 2017 136:367-383. doi: 10.1161/CIRCULATIONAHA.117.028388.

7.3 Molecular mechanisms of ovarian ageing and menopause

Co-Supervisor 1: Dr Kim Jonas
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Project description:

Ovarian ageing is a naturally occurring process that results in a gradual decline in ovarian function and cessation at menopause. In addition to declining fertility, ovarian ageing results a number of metabolic and cognitive changes which increase the risk for development of multiple disorders including osteoporosis and heart disease. Moreover, for 1 in 100 women under the age of 40, premature ovarian ageing can occur with unknown aetiology in most cases. However, our understanding of the mechanisms governing ovarian ageing remains limited, highlighting an unmet need for novel discoveries in this area. The overarching aim of this project is to identify novel gene expression changes that occur during ovarian ageing and determine their role in this process. This project will utilise human ovarian cells to determine key ovarian gene expression changes that occur with ageing (Yr1). Validation and experimental testing of highlighted genes/pathways will be carried out using human ovarian cells from patients with normal and diminished ovarian reserves, and in vivo animal models (Yr2-3).

A variety of molecular and physiological techniques will be utilised throughout the project including RNAseq, gene knockdown and overexpression, 2D cell and 3D organoid cultures, qPCR, Western blotting, immuno-cyto/histochemistry, microscopy- confocal and potentially super resolution imaging. Full training will be provided in supervisors' well-equipped research laboratories. The student will have access to KCL core and BRC facilities (e.g. Nikon Imaging Centre and BRC Flow cytometry and genomics platforms) and receive relevant personal development training, journal clubs and seminars.

Representative publications:

- **Jonas KC,** et al Temporal reprogramming of calcium signalling via crosstalk of gonadotrophin receptors that associate as functionally asymmetric heteromers. Sci Rep. 2018;8(1):2239. doi: 10.1038/s41598-018-20722-5
- Noli et al.: Effects of thyroid hormone on mitochondria and metabolism of human preimplantation embryos. Stem Cells 2020;38:369-381. doi: 10.1002/stem.3129

8.3 integrating cardiorespiratory variables into clinical management of pregnancy in low-, middle- and high-income countries

Co-Supervisor 1: Prof Laura A Magee
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Project description:

Blood pressure (BP) is key to maternity care elevated BP (systolic BP [sBP] ≥140mmHg or diastolic BP [dBP] ≥90mmHg), is associated with increased actuarial risks for adverse maternal and perinatal events. There is emerging evidence that other markers of cardiorespiratory function (e.g., BP variability, prehypertension (sBP 130-139mmHg or dBP 80-89mmHg), heart rate, respiratory rate, and pulse waveform (photoplethysmography) may be markers of maternal and perinatal risk. Patterns of risk may differ between low- and middle-income (LMICs) and high-income countries (HICs), and may identify intermediate- and long-term risks for women and children.

Methods: The PhD candidate has access to a series of informative datasets (>130,000 total pregnancies). HIC datasets: ALSPAC (1991-92), Fetal Medicine Foundation (2000-ongoing), eLIXIR (2018-ongoing), and the K2 Hampton BP app (pregnancies, 2018-ongoing). LMIC datasets: CLIP Trials (2014-16 [Pakistan, India, Mozambique]) and PRECISE Network (2019-ongoing [The Gambia, Kenya, Mozambique]). Approval pending (>25,000 pregnancies): Southampton Women's Survey (1998-2002) and Born in Bradford (2007-10). With statistical and engineering co-supervisory support from Strathclyde University and KCL, the candidate will learn to (i) assemble and manipulate complex datasets, (ii) use univariable analyses, logistic regression modelling, and machine learning to develop models that describe relationships between variables and maternal, fetal, and neonatal outcomes; (iii) integrate models to develop a digital health tool, INTEGRATE; and (iv) usability test INTEGRATE.

Objectives:
Yr1: Database assembly and BP level and variability and heart rate models
Yr2: Respiratory rate and photoplethysmography models
Yr3: INTEGRATE tool development and usability testing.

Translational potential:
INTEGRATE LMIC and HIC implementation trials.

Representative publications:

- **Magee LA**, Singer J, Lee T, McManus RJ, Lay-Flurrie S, Rey E, Chappell LC, Myers J, Logan AG, von Dadelszen P. Are blood pressure level and variability related to pregnancy outcome? Analysis of control of hypertension in pregnancy study data. Pregnancy Hypertens. 2020;19:87-93.
- **von Dadelszen P**, Bhutta ZA, Sharma S, Bone J, Singer J, Wong H, Bellad MB, Goudar SS, Lee T, Li J, Mallapur AA, Munguambe K, Payne BA, Qureshi RN, Sacoor C, Sevene E, Vidler M, Magee LA;

CLIP Trials Working Group. The Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised trials in Mozambique, Pakistan, and India: an individual participant-level meta-analysis. Lancet. 2020;396(10250):553-563.

9.3 Identifying genetic factors that modulate the risk of secondary complications in Diabetes

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Project description:

Diabetes mellitus affects >400 million people worldwide and increases the risk of serious life-threatening complications, including cardiovascular disease, kidney failure and retinopathy. Chronic hyperglycaemia induces the generation of reactive oxygen species, key triggers of diabetic complications, implicating mitochondrial processes in disease progression. Mitochondria play a key role in cellular energy production, and even though they have their own compact genome, most mitochondrial processes are governed by nuclear encoded proteins. It is important to understand how the complex interplay between nuclear and mitochondrial genes influences risk of diabetic complications, and whether mutated mitochondrial DNA plays a causal role.

Objectives:

Year 1: Identify nuclear encoded mitochondrial genes whose expression is modified in individuals with diabetes.

Years 1&2: Integrate these data with tissue matched population level data to identify genetic modifiers of these genes.

Years 2&3: Use CRISPR combined with homologous recombination to introduce causal variants into relevant human cell lines to study their effects on mitochondrial function and cellular health. By using multi-dimensional data integration, it may be possible to use the outcomes of this study to stratify patients for risk of progressive disease such as diabetic cardiovascular disease or nephropathy. In addition, this work could be utilised to evaluate personalised treatment efficacy based on organ specific protection of mitochondria in patients with diabetes.

This project will provide the student with excellent training in the analysis of high-throughput sequencing data, bioinformatics (including programming), genomic analysis and molecular and cell biology techniques to understand fundamental disease processes with high impact on human health.

Representative publications:

- Czajka, A., Ajaz, S., Gnudi, L., Parsade, C. K., Jones, P., Reid, F. & **Malik, A. N** 2015. Altered Mitochondrial Function, Mitochondrial DNA and Reduced Metabolic Flexibility in Patients With Diabetic Nephropathy,: EBioMedicine. 2, 6, p. 499-512
- Ali, A.T., Boehme, L., Antona, G-C, Seitan, V.C., Small, K.S., **Hodgkinson, A**. 2019. Nuclear Genetic Regulation of the Human Mitochondrial Transcriptome. eLife 8: e41927.

10.3 Using machine learning to predict treatment pathways in end stage kidney disease (ESKD) in the context of Covid-19

Co-Supervisor 1: Mariam Molokhia
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Project description:

Background: Chronic kidney disease (CKD) is common, and increases with age. In some patients, kidney function continues to slowly decline, resulting in end stage kidney disease (ESKD). Patients with ESKD are either managed conservatively or receive dialysis and the project aims to better understand predictors of these treatment outcomes.

Investigation plan: This project will uniquely develop risk prediction algorithms for differentiating individuals for dialysis or comprehensive conservative care (CCC), with UKRR data, using machine learning (ML) methods. To inform the ML approach we will use KCL renal dataset and apply to the UKRR dataset. We will prospectively investigate patient outcomes in primary care (LDN) and during the COVID-19 epidemic.

Objectives:

1) To use a training dataset of ESKD individuals to develop algorithms predicting dialysis or CCC.
2) To use a training dataset to develop predictive outcome algorithms
3) To identify data items in the RenalWare (CKD data warehouse) which enhance algorithm accuracy.
4) To internally validate these algorithms using original dataset records.
5) To compare ML approaches with traditional statistical methods for modelling planned treatment.
6) To develop personalised risk prediction algorithms identifying treatment pathways.

ML approaches have been successfully used in risk prediction in hospital for acute kidney injury including neural network assessing sequential data inputs over time. Analyses will apply the artificial neural network (ANN) learning algorithm by fitting an optimized model to training data.
The project will compare traditional statistical methods and ANN methods and evaluate the robustness of each model in training and validation data cohorts.

Representative publications:

- Carr DF, Francis B, Jorgensen AL, Zhang E, Chinoy H, Heckbert SR, Bis JC, Brody JA, Floyd J, Psaty BM, **Molokhia M**, Lapeyre-Mestre M, Conforti A, Alfirevic A, van Staa T, Pirmohamed M. Genome-wide association study of statin-induced myopathy in patients recruited using the UK clinical practice research datalink. Clin Pharmacol Ther. 2019 Jun 20. doi: 10.1002/cpt.1557. PMID: 31220337.

- iRDA: a new filter towards predictive, stable, and enriched candidate genes. Lai HM, Albrecht AA, **Steinhöfel KK.** BMC Genomics. 2015 Dec 9; 16 (1041): https://doi.org/10.1186/s12864-015-2129-5. PMID: 26647162.

11.3 Trans-Generational Transmission of Obesity and Obesity-induced Liver Disease: a role for maternal vaginal microbiota?

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Project description:

The United Kingdom adult population prevalence of obesity is 30%, with 30% of children overweight or obese. We have recently shown, that the offspring of obese mothers have increased appetite, body weights, fat mass and markers of obesity-induced liver disease (non-alcoholic fatty liver disease, NAFLD) compared with offspring of lean mothers.

It is likely that transmission of obesity from mother to offspring during peri-natal and post-natal periods is at least partially via the transmission of maternal microbiota to the newborn. The aim of this project is to determine the mechanisms by which this trans-generational transmission of obesity and NAFLD occur, using the following over-arching objectives and training opportunities in the consequent experimental methods and techniques:

Year 1: Experimental design and assembly of a study population of breeding mice. Bioinformatic assessment of microbial community composition by metagenomic sequencing of the 16s rDNA amplicon in the maternal vagina and offspring gut. Collection of liver, serum, urine and feces samples for subsequent analyses.
Year 2: Changes in liver physiology will be elucidated through tissue histology and identification of proteins with enriched expression in the liver biopsy material. The liver specific proteome measured by quantitative mass spectrometry proteomics methods will be further defined by transcriptomics.
Year 3: Exploration of metabolites putatively involved in NAFLD will be determined by their extraction from blood, feces and urine samples for metabolic profiling analysis using nuclear magnetic resonance (NMR) spectroscopy.
Year 4: Consolidation of microbiome, tissue histology, transcriptome, proteome and metabolome results, thesis defence and dissemination of results.

Representative publications:

- Mouralidarane A1, Soeda J, Visconti-Pugmire C, Samuelsson AM, Pombo J, Maragkoudaki X, Butt A, Saraswati R, Novelli M, Fusai G, Poston L, Taylor PD, **Oben JA.** (2013), Maternal obesity programs offspring nonalcoholic fatty liver disease by innate immune dysfunction in mice. Hepatology. 58:128-38. doi: 10.1002/hep.26248. With Editorial

- Gacesa R, Hung Y-H, Bourne DG, **Long PF**. Horizontal transfer of a natterin-like toxin encoding gene within the holobiont of the reef building coral Acropora digitifera (Cnidaria: Anthozoa: Scleractinia) and across multiple animal linages. J Ven Res 2020 10:7-12.

12.3 Islet GPCR regulation by GRKs and RGS proteins

Co-Supervisor 1: Prof Shanta Persaud
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Project description:

Over 400 million people worldwide currently have type 2 diabetes (T2D), in which peripheral cells show reduced sensitivity to insulin and islet beta-cells do not secrete sufficient insulin to maintain low blood glucose levels. Declining beta-cell number is the fundamental problem in T2D but none of the current pharmacotherapies therapies effectively increase functional beta-cell mass. G-protein-coupled receptors (GPCRs) are the targets for many clinically used therapeutics, and our "GPCRome" mapping has indicated that human islets express nearly 300 GPCRs, at least some of which could be harnessed therapeutically to treat T2D. GPCRs are phosphorylated by GPCR kinases (GRKs) following agonist binding and this reduces G-protein coupling of active GPCRs. Regulator of G-protein signalling (RGS) proteins provide another level of GPCR regulation by binding to Ga-GTP to increase GTP hydrolysis and terminate signalling. Very little is known about GRK and RGS expression and function in islets and this will be examined in this project to better understand the potential of targeting islet GPCRs to treat T2D.

Overarching Objectives and Skills Training:

This project has 4 main objectives:

1. Determine the effects of selective RGS and GRK inhibitors (e.g. CCG50014; CMPD101) on GPCR agonist-regulated islet function (islet isolation; quantification of cAMP, IP1 and Ca2+; insulin secretion; BrdU incorporation and caspase assays)
2. Quantify mRNAs encoding GRKs and RGS proteins in human islets from low and high BMI donors and determine changes that occur under conditions of obesity (RNA extraction; RT-qPCR)
3. Identify cellular localisation of RGS proteins and GRKs in pancreas samples from lean and obese humans and mice (fluorescence IHC and image analysis)
4. Determine effects of deleting key GRKs and RGS protein in beta-cells (CRISPR-Cas9 gene editing, cell culture, functional assays)

Representative publications:

- Atanes P, Ruz-Maldonado I, Hawkes R, Liu B, Zhao M, Huang GC, Al-Amily IM, Salehi A, Amisten S and Persaud SJ (2018) Defining G-protein coupled receptor peptide ligand expressomes and signalomes in human and mouse islets. Cell. Mol. Life Sci. 75, 3039-3050

- Rackham CL, Vargas AE, Hawkes RG, Amisten S, Persaud SJ, Austin AL, King AJ and Jones PM (2016) Annexin A1 is a key modulator of mesenchymal stromal cell-mediated improvements in islet function. Diabetes 65, 129-39

13.3 NMRK2 in NAD+ homeostasis in health and heart failure: From molecules to animals – an interdisciplinary study

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Project description:

Loss of NAD+ homeostasis is a key feature of many cardiomyopathies and a hallmark of end stage heart failure. Already at an early stage of DCM, NAD+ levels are down by about 30%. A key enzyme in its regulation, NMRK2, is vastly upregulated in a mouse model of early stage DCM and a zebrafish model for force dependent regulation of gene expression. In addition to its enzymatic properties NMRK2 also appears to be involved in force dependent regulation by an interaction with integrins. We aim to study NMRK2 both in vitro and in vivo by combining the experience of the Hughes lab with the zebrafish model system and the Pfuhl lab with biophysics and structural biology. In this way structure and enzyme mechanism will be studied in the context of the whole animal and findings of one approach can be swiftly tested and validated using the other approach.

The project has three aims:

1. Characterisation of NMRK2 activity, mechanism and regulation in vitro and in vivo.
2. Determination of the structure of NMRK2 and an exploration of its splice isoforms.
2. Exploration of the effect of integrin binding to NMRK2 on localisation and activity of the enzyme.

The student will be exposed to standard techniques for biochemistry and biophysics such as bacterial protein expression and purification followed by functional and structural studies. For the in vivo experiments the student will learn standard zebrafish techniques including methods for genetic manipulation.

Representative publications:

- M. Zaleska, C. Fogl, A. L. Kho, A. Ababou, E. Ehler, **M. Pfuhl**, "The Cardiac Stress Response Factor Ms1 Can Bind to DNA and Has a Function in the Nucleus", PLoSONE DOI: 10.1371/journal.pone.014461410, 2015
- Osborn*, D.P.S., Li*, K., Cutty, S.J., Nelson, A.C., Wardle, F.C., Hinits, Y. and **S.M. Hughes** (2020) Fgf-driven Tbx protein activities directly induce myf5 and myod to initiate zebrafish myogenesis. Development 147: dev184689 doi: 10.1242/dev.184689. PMID: 32345657

14.3 Platelets and allergen sensitization: A critical interface between trained innate immunity and the adaptive immune response.

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Project description:

Background: Platelets have been recognized for some time to act as inflammatory cells in the defence of the body against infection, performing many functions normally associated with leukocytes. These roles are distinct from platelet function during haemostasis. Interestingly, platelets act as a 'bridge' between the innate and adaptive immune response. Platelets are activated in patients with asthma, and are responsible for the misdirected inflammatory response. Recently, we reported that platelets migrate into lung tissue upon allergen sensitization and challenge and associate with lung dendritic cells (DCs), and that temporary platelet depletion at the time of initial allergen sensitization resulted in reduced inflammatory responses upon subsequent, secondary allergen exposure. We outline a PhD programme to investigate how the process of antigen sensitization affects platelet production and activity and the development of immune memory. Future impact might lead to alternative strategies for 'disease modifying' therapies of allergic disease or infections.

Details of Techniques: In vivo skills pertinent to murine models of allergic lung inflammation. An exciting research avenue is advanced real time imaging techniques to record, for example, lung platelet production and DC interactions in mice (with collaborators at University California San Francisco). In vitro functional assays to elucidate platelet activation, function, and interactions with innate immune cells (e.g. flow cytometry, chemotaxis).

Objectives:
Year 1. How does antigen exposure modulate platelet production and phenotype?
Year 2. How do platelets stimulate innate immune cells, their tissue recruitment and transit?
Year 3-4. How do platelets modulate antigen sensitization and recognition?

Representative publications:

- Amison RT et al. Platelets play a central role in sensitisation to allergen. Am J Respir Cell Mol Biol. 2018. 59: 96-103.
- **Amison RT** et al. Platelet depletion impairs host defence to pulmonary infection with Pseudomonas Aeruginosa in mice. Am J Respir Cell Mol Biol. 2018; 58:331-340.

15.3 Impact of critical care on skeletal muscle strength

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Project description:

Skeletal muscle wasting and weakness occurs in up to 65% of ICU patients and is a major complication of critical illness. Intensive care unit-acquired weakness (ICU-AW) influences not only short term but also long-term clinical outcomes, contributing to 'post intensive care syndrome' a collection of common health disorders of which muscle weakness is a significant component. Muscle force generation is influenced by multiple factors and while the anatomical and physiological characteristics of muscle itself are significant determinants of strength, the central nervous system also plays an important role.

Research examining ICU-AW has focused primarily on peripheral neuromuscular function while much less is known regarding potentially important neurological changes within the central nervous system (CNS). Studies in healthy subjects employing short periods of limb immobilisation have described decrements in muscle strength greater than that expected from the degree of muscle atrophy observed. Such reductions in strength are, therefore, potentially due to reduced neural drive to the muscle from the CNS.

The proposed study examines the impact of critical illness on muscle strength and central nervous system and motor cortex function in patients following critical illness in relation to ICU-AW. Training in a broad range of human physiological technique to assess muscle strength and architecture and physical function will be provided including electrical and magnetic motor nerve stimulation and force assessment as well as transcranial magnetic stimulation. Year 1 training, study setup and commencement of data acquisition in controls. Year 2 - 3 patient data acquisition. Year 3-4 completion of data acquisition and PhD thesis preparation

Representative publications:

- Connolly B, Maddocks M, MacBean V, Bernal W, Hart N, Hopkins P & **Rafferty GF**. (2018). Nonvolitional assessment of tibialis anterior force and architecture during critical illness. Muscle Nerve 57, 964-972.
- Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Phadke R, Dew T, Sidhu PS, Velloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SD, **Hart N** & Montgomery HE. (2013). Acute skeletal muscle wasting in critical illness. JAMA 310, 1591-1600.

16.3 Characterisation of a unique stem cell niche that regulates vascular calcification and bone formation

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Project description:

'Hardening of the arteries' or vascular calcification (VC) is a ubiquitous feature of cardiovascular ageing that often occurs concomitantly with osteoporosis. VC is a cell mediated process driven by vascular smooth muscle cells (VSMCs) which convert to osteochondrogenic cells by upregulating Runx2 and Sox9, two master regulators of bone and cartilage differentiation. Recently we have discovered a stem cell niche that is common to VSMCs and bone and that is a critical regulator of vascular calcification. Specifically using 2 different smooth muscle specific Cre lines to delete Runx2 in the vasculature we found that one line of mice exhibited skull and tooth defects and accelerated vascular ageing, while the other line had normal bone formation, was resistant to vascular calcification and aged normally. This project combines the expertise of bone and vascular biologists to now identify and characterise this novel stem cell niche and its contribution to vascular and bone development as well as ageing.

Aims:

Years 1 & 2. Cell fate mapping with a mTmG reporter mouse to determine the origin of the VSMCs and their contribution to bone and vascular development.

Years 1 & 2. We will determine the specific roles of Runx2 versus Sox9 in bone and vascular development/function using the 2 VSMC-specific Cre's to knockout Runx2 and Sox9 phenotyping the mice using cellular, imaging and physiological techniques.

Year 2 and 3. We will use comparative RNA-seq to examine the transcriptional differences between the vascular niches for young and old Runx2 and Sox9 knockout mice comparing the two different Cre's to determine the genes driving vascular ageing phenotypes.

Techniques: Animal husbandry, cell tracking, confocal microscopy, bone phenotyping (microCT), vascular phenotyping (blood pressure, pulse wave velocity), histology, tissue culture, molecular biology, bioinformatics.

Representative publications:

- Müller KH, Hayward R, Rajan R, Whitehead M, Cobb AM, Ahmad S, Sun M, Goldberga I, Li R, Bashtanova U, Puszkarska AM, Reid DG, Brooks RA, Skepper JN, Bordoloi J, Chow WY, Oschkinat H, Groombridge A, Scherman OA, Harrison JA, Verhulst A, D'Haese PC, Neven E, Needham LM, Lee SF, **Shanahan CM***, Duer MJ*. Poly(ADP-Ribose) Links the DNA Damage Response and Biomineralization. Cell Rep. 2019 Jun 11;27(11):3124-3138. (*equal contribution).

- Crespo-Enriquez I, Hodgson T, Zakaria S, Cadoni E, Shah M, Allen S, Al-Khishali A, Mao Y, Yiu A, Petzold J, Villagomez-Olea G, Pitsillides AA, Irvine KD, **Francis-West P**. Dchs1-Fat4 regulation of osteogenic differentiation in mouse. Development. 2019 doi: 10.1242/dev.176776).

17.3 Creating a rationale for personalised spontaneous-preterm-birth risk management - an in vitro model of bacteria-host innate immune interactions in the reproductive tract

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Project description:

The cervicovaginal environment (microbiome, innate immune system, and metabolome) is an important contributor to a healthy pregnancy. Risk of premature birth is associated with changes in resident microbial community, altered immune responses and inflammation. We hypothesise that the resultant inflammation affects vaginal epithelia and cervix integrity and increases risk of ascending infection. In clinical studies, we have identified a panel of metabolites and bacteria that can predict spontaneous preterm birth in UK women; we are validating this in a separate sub-Saharan Africa cohort. These studies give insight into the pregnant cervicovaginal environment as well as providing biological samples for mechanistic studies.

This laboratory-based PhD will investigate the impact of an altered cervicovaginal environment on epithelial cell function and immune response in the presence and absence of bacteria/bacterial products of metabolism. The overarching goal is to inform the future use of targeted probiotics and/or antibiotic strategies to prevent preterm birth.

Specific aims are to:

1. Determine the impact of metabolites and bacterial products on vaginal epithelial cell integrity and inflammation using a 3D cell model
2. Develop the cell model to enable co-culture with specific immune cells and/or bacterial isolates
3. Explore the synergistic interactions between key bacteria isolated from pregnant women, their impact on vaginal epithelial cell culture (aim 1), and sensitivity to antibiotics

Skills/techniques to be acquired: 3D vaginal epithelial cell culture, multiplex ELISA, NMR, microbiological techniques, molecular techniques (PCR, QPCR, and RNAseq), statistics and bioinformatic analytical pipelines. The student will also develop a range of transferable academic skills.

Representative publications:

- Hezelgrave NL, Seed PT, Chin-Smith EC, Ridout AE, Shennan AH, **Tribe RM**. Cervicovaginal natural antimicrobial expression in pregnancy and association with spontaneous preterm birth. Sci Rep. 2020; 10:12018. https://doi.org/10.1038/s41598-020-68329-z
- Wang, Y., Leong, L.E.X., Keating, R.L., Kanno, T., Abell, G.C., Mobegi, F., Choo, J.M., Wesselingh, S.L., **Mason, A.J.**, Burr, L.C. & Rogers, G.B. Opportunistic bacteria confer the ability to ferment prebiotic starch in the adult cystic fibrosis gut. Gut Microbes 2019 (10:3) 367-381

18.3 “Use it or lose it”: Understanding age-related changes in skeletal muscle protein turnover in response to exercise, nutrition and pharmacological interventions.

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Project description:

All over the world people are living longer with a higher incidence of chronic health conditions. Ageing is the greatest risk factor for many life-threatening disorders. Skeletal muscle wasting conditions that accompany ageing and/or disease, such as sarcopenia and cancer cachexia, lead to a decline in metabolic health and functional capacity, and increased risk of morbidity and mortality.

A fundamental cause of muscle wasting includes a reduction in skeletal muscle protein synthesis rates in response to exercise and nutrition. This phenomenon has been extensively characterised on a global level, i.e. when all muscle proteins are combined. Limited information exists regarding changes in synthesis rates of individual, functionally distinct (i.e. contractile vs. mitochondrial) muscle proteins. This level of detail is critical to, (a) advance understanding of the biological mechanisms that underpin the (musculoskeletal) ageing process, and (b) identify novel and targeted non-pharmacological (exercise, leucine ingestion) and pharmacological interventions (senolytics) to counteract musclewasting.

We will fill this gap in knowledge by utilising state-of-the-art techniques such as deuterium oxide isotope tracers and proteomics to:
1. Determine changes in global and individual muscle protein synthesis rates between young, middle-aged, and older adults (Years 1 & 2).
2. Investigate the impact of senolytic interventions in modulating changes in synthesis rates of individual muscle proteins across the life course (Years 2 & 3). Skills training embedded within this multi-disciplinary project will include stable isotope (deuterium) tracer methodology (ESPEN intensive course https://www.espen.org/education/espen-courses, proteomics (KCL Centre of Excellence for Mass Spectrometry) and MRI scanning.

Representative publications:

- Damas F, Angleri V, Phillips SM, **Witard OC**, Ugrinowitsch C, Santanielo N, Soligon SD, Costa LAR, Lixandrão ME, Conceição MS, and Libardi CA. Myofibrillar protein synthesis and muscle hypertrophy individualized responses to systematically changing resistance training variables in trained young men. J Appl Physiol (1985). 2019 Sep 1;127(3):806-815. doi: 10.1152/japplphysiol.00350.2019.
- 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 J, **Ellison-Hughes GM**. (2019) Aged-senescent cells contribute to impaired heart regeneration. Aging Cell. 18: e12931. DOI: 10.1111/acel.12931.