Theme 3 Physiological Medicine

2018/2019

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 **MRCDTP2018_Theme3**

Application Deadline: Sunday 26th November
Shortlisted candidates will be contacted in mid-January.

Interviews: 31st January & 1st February 2018
The 2018/19 studentships will commence in September 2018.

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 What are the cardio-metabolic effects of industrially modified saturated fats?

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Co-Supervisor 2: Dr Wendy Hall
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Project description:

Scientific basis: Saturated fats are commonly modified by the food industry using the process of interesterification (whereby fatty acids are rearranged on the glycerol backbone of triacylglycerols), to create fats with desirable functional (e.g. melting) characteristics for applications in spreads and bakery products. Commercially, stearic or palmitic acid rich fats are interesterified (IE), however the effects of these commonly consumed IE fats and their differences on cardio-metabolic disease is unknown. There is evidence however that stearic acid has a neutral effect on blood cholesterol compared to the cholesterol-raising capacity of palmitic acid. This research aims to investigate the effect of IE stearic versus palmitic acid rich fats on physiological processes underpinning cardio-metabolic risk in a systematic chronic human metabolic randomised controlled trial, including; postprandial lipid metabolism, vascular function, insulin sensitivity and inflammation to investigate their cardio-metabolic health effects.

Objectives: Human study 1 (year 1-2) will investigate the chronic and postprandial cardio-metabolic effects of the most commonly consumed IE palmitic versus stearic acid rich fats blends in a randomised controlled trial in healthy participants. Mechanisms underpinning differential responses will be studied using specialist analytical and physiological techniques.

Human study 2 (year 2/3-3.5) will investigate the effects of different doses (as consumed) of these of commonly consumed fats on postprandial lipaemia, lipoprotein metabolism, and markers of endothelial function.

Skills: The student will be trained in running human metabolic studies (ethical approval, recruiting, screening, day to day running of a trial, data analysis and report writing) and performing specialist lipid analysis (gas liquid chromatography, NMR spectroscopy) and vascular ultrasonography.

Two representative publications:
1. Hall, W, Iqbal, S., Li, H., Gray, G. & Berry, S. Modulation of postprandial lipaemia by a single meal containing a commonly consumed interesterified palmitic acid-rich fat blend compared to a non-interesterified equivalent. Eur J Nutr 2016. doi:10.1007/s00394-016-1284-z.
2. Hall, W., Fiuza Brito, M., Huang, J., Wood, L., Filippou, A., Sanders, T. A. B. & Berry, S. An interesterified palm olein test meal decreases early-phase postprandial lipemia compared to palm olein: a randomized controlled trial. 2014. Lipids. 49, 895-904.

2.3 Modulating beta-cell iron levels to treat type 2 diabetes

Co-Supervisor 1: Dr Paul Caton
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Project description:

Modulating beta-cell iron levels to treat type 2 diabetes
Prevalence of type 2 diabetes (T2D) has increased dramatically in recent years. Reduced beta-cell function and mass are central to the development of T2D. Elucidating the underlying pathophysiology is crucial in order to devise novel strategies to prevent and treat T2D.

This project will investigate the role of excessive iron levels in the beta-cell as a central factor mediating beta-cell failure in T2D.

Our previous work has suggested that excess iron levels, via the actions of a protein called lipocalin-2, play a key role in beta-cell failure in T2D. In addition, evidence suggests a role for reduced iron and lipocalin-2 levels as mediators of the beneficial effects of bariatric surgery on T2D. This project will expand on these findings to determine the precise mechanistic role of iron-mediated beta-cell failure in T2D. Understanding this pathway may lead to development of novel nutritional advice and treatment targets for T2D.

Skills training: Cell culture, islet isolation, radioimmunoassay of insulin secretion, luminescence apoptosis and viability assays, BrdU proliferation assays; qRT-PCR, microscopy/immunofluorescence, western blot, in vivo mouse phenotyping (glucose metabolism, islet function).

Objectives:

Year 1: Characterise the effects of elevated iron/lipocalin-2 on mouse and human beta-cell function (insulin secretion) and mass (apoptosis, proliferation etc.)
Year 2: Determine the mechanisms of action of lipocalin-2 on β-cell function and mass
Year 3+: Examine the effects of excess iron/lipocalin-2 on beta-cell function and glucose homeostasis in mouse models. Measure changes in iron/lipocalin-2 in human bariatric surgery patient samples.

Two representative publications:
1. Kieswich J, Sayers SR, Silvestre MF, Harwood SM, Yaqoob MM, Caton PW (2016) Monomeric eNAMPT in the development of experimental diabetes in mice: a potential target for type 2 diabetes treatment. Diabetologia, 59(11):2477-86
2. Lesjak M, Hoque R, Balesaria S, Skinner V, Debnam ES, Srai SK, Sharp PA. (2014) Quercetin inhibits intestinal iron absorption and ferroportin transporter expression in
vivo and in vitro. PLoS One. 4;9(7):e102900.

3.3 Therapeutic potential of Sulforaphane-induced Nrf2 activation to protect pre-eclamptic fetal endothelial cells

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Co-Supervisor 2: Prof Giovanni E. Mann
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Project description:

Pre-eclampsia (PE) is defined as the development of hypertension and proteinuria during pregnancy. Children of PE mothers have raised blood pressure when compared to those from healthy pregnancies and are at greater risk of cardiometabolic disease in adulthood.

This project will study the role of the transcription factor NF E2-related factor 2 (Nrf2), a master regulator of antioxidant and phase II enzymes, in protecting PE fetal endothelial cells. Our previous work shows PE fetal endothelial cells fail to induce Nrf2 in response to endogenous oxidative stimuli and show elevated oxidative stress, which may prime the fetal vasculature towards later-life dysfunction. These findings of impaired Nrf2 activation in PE are similar to those we report in diabetic fetal endothelial cells, with our latest findings demonstrating we can restore Nrf2 defenses by pre-treating diabetic cells with a potent dietary Nrf2 inducer sulforaphane (SFN).

This studentship will use a range of molecular biology techniques already established in the Chapple and Mann laboratories to characterise (1) the mechanism(s) by which Nrf2 activation is impaired in PE by focusing on well-known Nrf2 regulators (e.g. DJ-1, GSK3β and Bach1) and (2) whether SFN pre-treatment restores Nrf2 defences and alleviates markers of cellular damage.

This work may lead to a novel therapy to protect mother and child against later-life cardiometabolic complications and fits well with Dr Chapple's and Prof Mann's core research theme of investigating dietary agents to protect against adverse pregnancy and ageing using both in vitro and in vivo models.

Two representative publications:

1. Chapple SJ*, Keeley TP, Mastronicola D, Arno M, Vizcay-Barrena G, Fleck R, Siow RC, Mann GE (2016) Bach1 differentially regulates distinct Nrf2-dependent genes in human venous and coronary artery endothelial cells adapted to physiological oxygen levels. Free Radicals in Biology Medicine. 92:152-62
2. Cheng X*, Chapple SJ*, Patel B*, Puszyk W, Sugden D, Yin X, Mayr M, Siow RC, Mann GE (2013) Gestational diabetes mellitus impairs Nrf2-mediated adaptive antioxidant defenses and redox signaling in fetal endothelial cells in utero. Diabetes 62(12):4088-97

4.3 AAV-mediated gene therapy approaches to promote cardiac regeneration after myocardial infarction.

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Project description:

Acute myocardial infarction (AMI), caused by occlusion of the coronary arteries, typically results in significant cardiomyocyte cell death and irreversible remodeling, which eventually leads to chronic heart failure. The recognition that cardiomyocytes have limited regenerative potential has instigated the development of novel gene therapy approaches that are aiming to stimulate this intrinsic proliferation potential.
Cardiac gene transfer of protein coding genes that influence the cell cycle of cardiomyocytes holds potential for novel therapeutics that target cardiac regeneration.

The laboratory of Prof. Shah has recently demonstrated that a reactive oxygen species-generating protein NADPH oxidase-4, Nox4, is able to increase the proliferation of cultured neonatal cardiomyocytes. Furthermore, they have shown that cardiac-specific overexpression of Nox4 in mice in vivo can lead to increased cardiomyocyte numbers without affecting normal heart structure and function.

The proposed project is designed to explore the efficacy of AAV-mediated Nox4 gene therapy for the treatment of AMI and tackle key challenges relating to translation into future therapies. The student will learn a wide variety of skills ranging form the assessment of normal heart physiology and cardiovascular disease to basic AAV biology and AAV gene therapy.

Aim 1: To generate various Nox4 AAV vectors and assess efficacy in mouse models of AMI
Aim 2: To design a cardiotropic vector that is optimised for human transduction
Aim 3: To demonstrate pre-clinical proof-of-concept of this novel approach

Two representative publications:
1. Santos CXC, Hafstad AD, Beretta M, Zhang M, Molenaar C, Kopec J, Fotinou D, Murray TV, Cobb AM, Martin D, Silva MZ, Anilkumar N, Schröder K, Shanahan CM, Brewer AC, Brandes RP, Blanc E, Parsons M, Belousov V, Cammack R, Hider RC, Steiner RA, Shah AM. Targeted redox inhibition of protein phosphatase 1 by Nox4 regulates eIF2α-mediated stress signaling. EMBO J. 2016;35:319–334.
2. Identification of a Functionally Relevant Adeno-Associated Virus Rep68 Oligomeric Interface.
Bardelli M, Zárate-Pérez F, Agúndez L, Linden RM, Escalante CR, Henckaerts E.
J Virol. 2016 Jul 11;90(15):6612-24. doi: 10.1128/JVI.00356-16.

5.3 Strategies to improve islet transplantation outcomes

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Project description:

Islet transplantation as a treatment for Type 1 diabetes can stabilise blood glucose concentrations and protect against hypoglycaemia. However, only half of patients undergoing the procedure become insulin independent. This project aims to understand the dynamics of islet function after transplantation by using novel glucose sensors in a variety of rodent transplantation models. Using this state of the art continuous glucose monitoring technology will allow treatments that have previously shown potential in rodent models to be fully optimised to improve islet transplantation outcome in humans. Initially we will assess the effect of transplantation site on blood glucose excursions in vascularised and non-vascularised islet transplantation models. We will then assess at which stage of the transplantation treatments such as GLP-1 receptor agonists are most beneficial. We will use this information to translate our findings to human islet transplantation. The two supervisors of this project are experts in preclinical and clinical islet transplantation respectively which will allow for rapid translation of our preclinical findings to clinical application. In the first year the student will be trained in rodent islet isolation, culture and transplantation. In the second year the student will carry out transplantation studies in rodents with state of the art continuous glucose monitoring to allow minute-by-minute visualisation of the effect of interventions on blood glucose concentrations. In the third year, the student will repeat the most promising studies with human islets in a rodent model and, if appropriate, become involved in the first proof of concept studies in humans.

Two representative publications:

1. Diabetes in rats is cured by islet transplantation... but only during daytime. King AJ, Austin AL, Nandi M, Bowe JE. In Press, Cell Transplant. Cell Transplant. 26:171-172, 2017.
2. Clinical use of continuous glucose monitoring in adults with type 1 diabetes
Slattery, D. & Choudhary, Diabetes Technology and Therapeutics. 19: S55-S61, 2017.

7.3 Exploring post-translational modifications of cardiac myosin binding protein C that guide the management of acute myocardial infraction

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Project description:

Many people seek medical help because they have chest pain and are worried they are having a heart attack (MI). The diagnosis of MI is made by measuring the release of a heart specific protein, called troponin (cTn) into the blood stream. We have discovered another protein, called cardiac myosin-binding protein C (cMyC), that seems better than cTn in separating those patients with MI from those without MI. At the moment, this separation is done using the concentration of cMyC in the blood stream. However, cMyC is phosphorylated and this change makes it resistant to proteases. Thus, the fragmentation pattern of cMyC may provide even more information to guide treatment than the concentration. This is very important since MIs are separated into type 1 and type 2, since they need very different treatments. Currently, there is no way to separate type 1 from type 2 MI other than doing an invasive coronary angiogram.
In this studentship, you will express full-length cMyC and expose it to the kinases that have been reported to cause its phosphorylation. The product of these in vitro kinase assays will be examined by mass spectrometry and other techniques to identify the sites (acceptor amino acids) and completeness (stoichiometry) of phosphorylation (yr 0.5). Recombinant cMyC completely phosphorylated at the relevant site(s) (and native, unphosphorylated control) will then be subjected to cleavage by the relevant proteases and the sequence of the resultant cMyC fragments analysed to determine if the sites, and their rates, of cleavage are altered (yr 1). Based on these experiments a new quantitive assay to measure cMyC fragments will be formulated and tested on blood samples from patients in whom the presence (and absence) of type 1 or type 2 MI has been rigorously adjudicated (>yr 1).

Two representative publications:
1. Marjot J, Kaier TE, Martin ED, Reji SS, Copeland O, Iqbal M, Goodson B, Hamren S, Harding SE, Marber MS. Quantifying the Release of Biomarkers of Myocardial Necrosis from Cardiac Myocytes and Intact Myocardium. Clin Chem. 2017;63(5):990-996.
2. Langley SR, Willeit K, Didangelos A, Matic LP, Skroblin P, Barallobre-Barreiro J, Lengquist M, Rungger G, Kapustin A, Kedenko L, Molenaar C, Lu R, Barwari T, Suna G, Yin X, Iglseder B, Paulweber B, Willeit P, Shalhoub J, Pasterkamp G, Davies AH, Monaco C, Hedin U, Shanahan CM, Willeit J, Kiechl S, Mayr M. Extracellular matrix proteomics identifies molecular signature of symptomatic carotid plaques.
J Clin Invest. 2017;127(4):1546-1560.

8.3 Drug Induced Liver Injury (DILI): Methods for developing and assessing translational risk prediction models using multi-dimensional data.

Co-Supervisor 1: Dr Mariam Molokhia
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Project description:

Drug induced liver injury (DILI) is a serious iatrogenic side-effect of many commonly used drugs, a common cause for post-marketing withdrawal and a leading cause of acute liver failure. Recently developed methods will be applied to derive improved models for DILI adverse drug reaction (ADR) personalised prediction from individual patient genetic, structural (peptide-HLA complex) and phenotypic data using specialised software and informatics platforms. This proposal will support more efficient methods of identifying key predictors of DILI in personalised and translational clinical medicine, with application to wider populations and other ADRs. Genetic and phenotypic data (Phase 1 IDILIC) from the International Serious Adverse Events Consortium (iSAEC) comprises 418 validated DILI cases, and matched controls, genotyped with Illumina 1M-Duo chips. We will validate the risk prediction in Phase 2 DILI studies, where 1079 well phenotyped cases and matched controls have been genotyped with Illumina HumanOmniExpress BeadChip, representing the largest international collection of validated DILI cases [highest drug burden due to co-amoxiclav, anti-tuberculosis drugs and flucloxacillin].

Skills training includes pharmacogenetics, epidemiological and statistical evidence synthesis, and analytical development using unique international datasets.

Objectives:
Yr1 To review published evidence for DILI risk factors.
Yr2 To create an integrated genetic environmental and clinical research data set using GWAS and other data from an international consortium for hepatotoxicity (DILI) to examine shared determinants of ADRs.
Yr3 To pilot and validate use of personalised risk prediction for DILI, using both genetic and non-genetic factors and examined using Receiver Operator Curves enabling population stratification for risk.

Two representative publications:
1. Nicoletti P, Aithal GP, Bjornsson ES, Andrade RJ, Sawle A, Arrese M, Barnhart HX, Bondon-Guitton E, Hayashi PH, Bessone F, Carvajal A, Cascorbi I, Cirulli ET, Chalasani N, Conforti A, Coulthard SA, Daly MJ, Day CP, Dillon JF, Fontana RJ, Grove JI, Hallberg P, Hernández N, Ibáñez L, Kullak-Ublick GA, Laitinen T, Larrey D, Lucena MI, Maitland-van der Zee AH, Martin JH, Molokhia M, Pirmohamed M, Powell EE, Qin S, Serrano J, Stephens C, Stolz A, Wadelius M, Watkins PB, Floratos A, Shen Y, Nelson MR, Urban TJ, Daly AK; International Drug-Induced Liver Injury Consortium, Drug-Induced Liver Injury Network Investigators, and International Serious Adverse Events Consortium. Association of Liver Injury From Specific Drugs, or Groups of Drugs, With Polymorphisms in HLA and Other Genes in a Genome-Wide Association Study. Gastroenterology. 2017 Apr;152(5):1078-1089. doi: 10.1053/j.gastro.2016.12.016. Epub 2016 Dec 30. PubMed PMID: 28043905; PMCID: PMC5367948.
2. Bernal W*, Wang Y*, Maggs J, Willars C, Sizer E, Auzinger G et al. Development and validation of a dynamic outcome prediction model for paracetamol-induced acute liver failure: a cohort study. The Lancet Gastroenterology & Hepatology. 2016 Nov;1(3):217-225. Available from, DOI: 10.1016/S2468-1253(16)30007-3, 10.1016/S2468-1253(16)30007-3 (*Joint first authors)

9.3 Maternal health, breast milk bioactives and infant growth

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Project description:

Maternal milk is a complex and dynamic fluid that provides nutrients, antigens, passive immunity, gut growth factors, and other bioactive compounds that can actively shape and educate the infant immune system. It is known that the immunological potential of human milk differs between mothers; however the control and regulation of the critical immune and other bioactive components of human milk is not well understood. A better understanding of how natural variation in these factors influences infant development, especially among nutritionally vulnerable populations, may inform the development of therapeutic and preventative strategies.

The aim of this project is to contribute to our understanding of the regulation of human milk bioactives and how variation in these components influences infant development. To meet this aim, the project will require access to relevant populations and training in laboratory techniques for sample analysis. Dr Moore is part of a BMGF-funded study to develop Reference Values for breast milk micronutrients (the MILQ study) using data and samples collected from mother-infant pairs in four contrasting settings (Gambia, Bangladesh, Brazil, Denmark). In each setting, detailed, longitudinal data and samples are being collected, including maternal and infant blood, breast milk, and detailed measures of infant growth and development. This studentship will utilise the already funded framework of MILQ to embed additional specific research questions, incorporating novel sample collection (e.g. maternal and infant stool samples/swabs for microbiome analysis) or sample analyses not currently included. The required training (laboratory, analytical) will be provided through existing collaborations within or outside of KCL.

Two representative publications:

1. Davis JC, Lewis ZT, Krishnan S, Bernstein RM, MOORE SE, Prentice AM, Mills DA, Lebrilla CB, Zivkovic AM. Growth and morbidity of Gambian infants are influenced by maternal milk oligosaccharides and infant gut microbiota. Sci Rep. 2017 Jan 12;7:40466. doi: 10.1038/srep40466.
2. Patel R, Moffatt JD, Mourmoura E, Demaison L, Seed PT, Poston L, Tribe RM. Effect of reproductive ageing on pregnant mouse uterus and cervix. J Physiol. 2017; 595:2065-208.4.

11.3 Targeting GPR56 to maintain islet beta-cell mass and function for diabetes therapy

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Project description:

Around 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. Pharmacotherapies for T2D stimulate insulin secretion, improve insulin sensitivity or increase glucose excretion. However, declining beta-cell number is the fundamental problem in T2D and none of the current therapies increase functional beta-cell mass. G-protein-coupled receptors (GPCRs) are the targets for many currently used therapeutics, and our "GPCRome" mapping has indicated that GPR56, an adhesion receptor, is the most abundant islet GPCR. We have used pancreases from wildtype and GPR56 knockout mice (E11-P9) to demonstrate that GPR56 deletion is associated with reduced islet mass and beta-cell number. Human embryonic and fetal pancreases (CS13-17wpc), available through the Human Developmental Biology Resource (HDBR), will be used in the current project. Overall, this PhD project will provide supporting data underpinning the development of GPR56 as a novel therapeutic to promote beta-cell development and function, to circumvent these deficits in T2D.

Overarching Objectives and Skills Training:
This project has 4 main objectives

1. Define the time-course of GPR56 expression during pancreas development in mice and humans, and compare with expression of endocrine progenitors (IHC using embryonic and fetal mouse and human pancreas; year 1)
2. Measure beta-cell apoptosis and proliferation following GPR56 deletion in mice, in vivo and in vitro (IHC, mouse islet isolation, apoptosis and viability assays, BrdU incorporation; years 1 and 2)
3. Identify the effects of the GPR56 peptide agonist TYFAVLM on mouse and human islet function (GTTs and ITTs, plasma insulin quantification, BrdU incorporation, islet isolation, insulin secretion and gene expression quantification; years 2 and 3).

Determine the requirement of GPR56 for normal glucose homeostasis (GTTs and ITTs in GPR56 KO mice fed normal chow and high fat diet, pancreas and islet histology, immunoassay; years 3 and 4).

Two representative publications:

1. Amisten S, Salehi A, Rorsman P, Jones PM, Persaud SJ (2013) An atlas and functional analysis of G-protein coupled receptors in human islets of Langerhans. Pharmacology & Therapeutics 139, 359-391

2. Rackham CL, Vargas AE, Hawkes RG, Amisten S, Persaud SJ, Austin AL, King AJ, Jones PM (2016) Annexin A1 is a key modulator of mesenchymal stromal cell-mediated improvements in islet function. Diabetes 65, 129-139

12.3 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.

Two representative publications:
1. Maddocks M, Jones M, Snell T, Connolly B, de Wolf-Linder S, Moxham J & Rafferty GF. (2014). Ankle dorsiflexor muscle size, composition and force with ageing and chronic obstructive pulmonary disease. Experimental Physiology 99, 1078-1088.

2. 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.
Joint Senior Authorship: Harridge-Hart-Montgomery

13.3 A role for the DNA damage response Arterial Calcification

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Website: http://www.kcl.ac.uk/lsm/research/divisions/cardio/about/people/clarkj.aspx

Project description:

Project description: Ageing is the strongest risk factor for cardiovascular (CV) disease and regeneration of aged tissue or maintenance of tissue health are key goals to combat vascular decline with age. Vascular calcification is a prevalent age-associated pathology leading to and arterial stiffening and heart remodelling. Recent data from our laboratory has shown than CV ageing mimics, in part, the ageing observed in patients with premature ageing diseases or progerias caused by defects in the nuclear lamina. Specifically we have shown that the accumulation of prelamin A, a toxic nuclear protein, drives CV ageing by accelerating DNA damage and senescence and this is associated with major changes in the epigenome of the cell. Importantly we have identified a number of drugs that can ameliorate these age associated defects in the epigenome and are effective in delaying calcification of vascular cells in vitro. We have also developed novel animal models of accelerated CV ageing and the aim of this project will be to: Test their efficacy of these novel compounds in delaying vascular ageing in these animal models in vivo (Year 1) and examine the mechanisms leading to attenuated ageing in vitro using cell biological techniques (Year 2) and in vivo using genetic crosses to animals deficient in the pathways identified (Years 3). This project will provide training in all aspects of molecular and cell biology including tissue culture, qRT-PCR, Western blot, confocal microscopy and epigenetics. The in vivo phase will train the student in vascular phenotyping including echocardiography, Flow Doppler, blood pressure measurement and histology/immunohistochemistry.

Two representative publications:

1. Liu Y, Drozdov I, Shroff R, Beltran LE, Shanahan CM. (2013). Prelamin A accelerates vascular calcification via activation of the DNA damage response and senescence-associated secretory phenotype in vascular smooth muscle cells. Circ Res 10;112(10):e99-109.
2. Aubdool, Aisah A; Thakore, Pratish; Argunhan, Fulye; Smillie, Sarah-Jane; Schnelle, Moritz; Srivastava, Salil; Alawi, Khadija M; Wilde, Elena; Mitchell, Jennifer; Farrell-Dillon, Keith; Richards, Daniel A; Maltese, Giuseppe; Siow, Richard C; Nandi, Manasi; Clark, James E; Shah, Ajay M; Sams, Anette; Brain, Susan D. A Novel α-Calcitonin Gene-Related Peptide Analogue Protects Against End-Organ Damage in Experimental Hypertension, Cardiac Hypertrophy and Heart Failure. . Circulation, 2017 doi: 10.1161/CIRCULATIONAHA.117.028388

14.3 Advanced Therapeutics for the domiciliary treatment of sleep apnoea using transcutaneous electrical stimulation

Co-Supervisor 1: Dr Joerg Steier
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Project description:

Scientific basis: Obstructive sleep apnoea (OSA) is the most common form of sleep disordered breathing, affecting at least 4% of the middle-aged male and 2% of the female population, its prevalence is rising with the current obesity epidemic. It leads to excessive sleepiness with physical, emotional and social impairment. The best treatment is continuous positive airway pressure (CPAP), but patients may not tolerate long-term CPAP treatment and compliance is limited.

Translational aspect: Alternative treatments to CPAP therapy are required. Most recently, a novel approach using hypoglossal nerve stimulation (HNS) with an implantable device has been approved. In parallel, our group has developed an approach using transcutaneous electrical stimulation of the upper airway. Both methods seem to achieve a similar effect size in selected patients, potentially improving long-term health outcomes.

Skills training: testing specifications of electrical stimulation and developing software algorithm; polysomnography; recording neural respiratory drive; volitional and non-volitional tests of respiratory muscle strength; electrical stimulation of human skeletal muscles; medical statistics; clinical trial coordination; health regulatory authority approvals.

Objectives: We propose to investigate and develop transcutaneous electrical stimulation of the upper airway in OSA by the following steps:
1) Identification of optimal stimulation settings, assessment of the upper airway dilator muscles' response and fatigue to electrical stimulation, (Year 1)
2) Phenotype characterization of responders and non-responders, functional determinants of response and adjustment of software algorithms for stimulation current, (Year 1-2)
3) Use of transcutaneous electrical stimulation, (Year 1-3)
4) Preparation of a definitive multi-centre trial in the community. (Year 2-4)

Two representative publications:
1. Pengo MF, Xiao S, Ratneswaran C, Reed K, Shah N, Chen T, Douiri A, Hart N, Luo YM, Rafferty GF, Rossi GP, Williams A, Polkey MI, Moxham J, Steier J. Randomised sham-controlled trial of transcutaneous electrical stimulation in obstructive sleep apnoea. Thorax 2016; doi:10.1136/thoraxjnl-2016-208691
2. Lee KK, Matos S, Evans DH, White P, Pavord ID, Birring SS. A longitudinal assessment of acute cough. Am J Respir Crit Care Med 2013;187(9):991-7.

15.3 Interventions to improve maternal metabolic profile in obese pregnancy and prevent cardio-metabolic and behavioural deficits in future generations.

Co-Supervisor 1: Dr Paul Taylor
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Project description:

Maternal obesity is now the single biggest obstetric risk factor, and it is now widely recognised that maternal obesity is not only a risk factor for pregnancy outcomes (e.g. pre-eclampsia, gestational diabetes and fetal macrosomia) but also for the long term health of the child, with increased risk of obesity and related comorbidities. Diet and nutrition in pregnancy are modifiable risk factors for offspring metabolic health and offer the opportunity for intervention to stem the growing tide of childhood obesity and impact on the cardiovascular and mental health of the next generation.

We have identified two candidate compounds, resveratrol and polydextrose which we intend to test for safety and efficacy (therapeutic potential) in a rat model of obesity in pregnancy. Resveratrol is a polyphenolic compound with numerous biological activities and anti-oxidant properties, found in high concentrations in the skins of red grapes. Polydextrose, on the other hand, is a soluble fibre with low glycaemic index and pro-biotic properties. The study will employ rodent models to advance understanding of the mechanism of action of these compounds in improving maternal metabolic profiles in obese pregnancy and their disease-preventive potential for cardiovascular (blood pressure) metabolic (obesity and diabetes) and behavioural deficits (cognitive function and ADHD) in future generations. Interventions with these two promising compounds, conceivably acting through divergent pathways, will also provide insight and mechanistic understanding of how obesity in pregnancy can beget cardio-metabolic disorders in childhood.

The studentship focuses on in vivo physiological techniques and is supported by an MRC Project grant.

Two representative publications:

1. Poston L & Taylor PD. Obesity in Pregnancy and the Legacy for the Next Generation. What Can we Learn from Animal Models? RCOG Obesity Study Group (2007).

2. Coen CW, Kalamatianos T, Oosthuizen MK, Poorun R, Faulkes CG & Bennett NC. Sociality and the telencephalic distribution of corticotrophin-releasing factor, urocortin 3, and binding sites for CRF type 1 and type 2 receptors: A comparative study of eusocial naked mole-rats and solitary Cape mole-rats. J Comp Neurol 2015, 523, 2344-2371.

16.3 Impact of progesterone and its metabolites on susceptibility to gestational diabetes mellitus.

Co-Supervisor 1: Prof Catherine Williamson
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Project description:

Normal gestation is associated with substantial changes in maternal metabolism including a marked increase in insulin resistance in later pregnancy. Gestational endocrine signals are likely to influence maternal insulin sensitivity and also the ability of the pancreas to secrete insulin to compensate for gestational insulin resistance. The supervisors are using a combination of in vivo murine models and human samples (in vivo dynamic tests and in vitro studies using intestinal explants and cell culture models) to evaluate the endocrine signals that cause women to be susceptible to gestational diabetes mellitus.

Hypotheses:

1. Elevated maternal progesterone levels cause altered signalling from the enteroendocrine cells of the intestine that result in insulin resistance
2. Progesterone and its metabolites signal via the receptors FXR and TGR5 to alter insulin secretion from beta cells of the pancreatic islets

In years 1-2 archived samples from human in vivo studies (blood sample collection following standardised meals and parallel evaluation of the gut microbiome/metabolites) will be studied. In vitro experiments will investigate mechanisms by which progesterone and its metabolites influence gut hormone release using human intestinal explants and the NCI-H716 cell line. The student will also study the impact of these hormones on islet function and insulin secretion. Subsequent experiments will evaluate the impact of endocrine signals on glucose metabolism in murine models of gestational diabetes mellitus (db/+ and high fat diet-fed mice). In the final years the student will evaluate drugs that impact enteroendocrine cell/islet function with the aim of preventing/delaying onset of gestational diabetes.*

Two representative publications

1. Papacleovoulou G, Nikolova V, Oduwole O, Chambers J, Vazquez-Lopez M, Jansen E, Nicolaides K, Parker M, and Williamson C. Gestational disruptions in metabolic rhythmicity of the liver, muscle and placenta affect fetal size. FASEB Journal 2017 April; 31(4): 1698-1708. PMID: 28082353.
2. Drynda, R., Peters, C.J., Jones, P.M., Bowe, J.E. The role of non-placental signals in the adaptation of islets to pregnancy. Hormone and Metabolic Research 2015 Jan; 47(1): 64-71. PMID: 25506682.

17.3 Improving islet transplantation using a rational gut hormone combination

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Co-Supervisor 2: **Dr. Tim Pullen**
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Project description:

The most common therapy for Type 1 diabetes is insulin administration. However, it is hard to mimic physiological insulin production with this strategy, leading to risk of hypoglycaemia and frequent glucose excursions which over time cause harmful complications. An alternative strategy is to transplant islets of Langerhans, an approved treatment for hypoglycaemia unawareness and brittle diabetes. Islet function and survival following transplantation is poor, few patients reach insulin independence on a single transplant. Improving islet function and survival would not only improve glycaemic control but increase the number of potential recipients. We have identified a new drug combination which both protects islets from damage and improves insulin secretion. One of the drugs activates neuropeptide Y receptors found on the islet and protects them from damage. It works particularly well when combined with glucagon-like peptide 1 (GLP-1), a well-known treatment for Type 2 diabetes. Our aim is to determine if this unique drug combination improves transplantation success.

The student will aim to answer the following: Are beta-cells functionally protected? does the combination work in human islets? what is the best dose combination? and how does the combination work? Islet cell damage will be assessed histologically and by caspase assay, islet secretory function by static and perifusion experiments. To understand mechanism, we will block signalling pathways using chemical and genetic means and interrogate important gene networks using next-generation sequencing. The student will use a minimal mass model (mouse and human islets) of transplantation to explore how the combination works.

Two representative publications

1. Franklin ZJ*, Tsakmaki A, Fonseca Pedro P, King AJ, Huang GC, Persaud SJ, Bewick. GA. Islet neuropeptide Y receptors are functionally conserved and novel targets for the preservation of beta-cell mass. Diabetes Obes Metab. 2017 Sep 22. doi: 10.1111/dom.13119
2. Pullen TJ, Huising MO, Rutter GA. Analysis of Purified Pancreatic Islet Beta and Alpha Cell Transcriptomes Reveals 11β-Hydroxysteroid Dehydrogenase (Hsd11b1) as a Novel Disallowed Gene. Front Genet. 2017 Apr 10;8:41. doi: 10.3389/fgene.2017.00041