# Theme 3
# Physiological Medicine

# 2020/2021

## 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

**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 The Benefits of Mycoprotein Consumption in the Regulation of Digestion and Nutrient Absorption: Implications for Gut Health and Metabolism.

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**Project description:**

With an increasing world population, the economic and environmental impact of increasing meat production and consumption is likely to become unsustainable. Multiple commercial strategies have arisen to combat this problem, including mycoprotein from Fusarium venevatum. Fungi are an excellent source of protein, low in fat and high in dietary fibre; however, apart from those who abstain from consumption of meat, consumer acceptance of processed mycoprotein remains low.

The dietary fibre component of mycoprotein sources may be important in the regulation of cholesterol homeostasis, post-prandial carbohydrate and fat digestion and absorption, and the maintenance of a healthy microbiome.

Specific objectives:

(1) Investigate the effect of processing on structural characteristics, rates of digestion and nutrient release using commercially available mycoprotein and its products compared to meat equivalents in vitro.

(2) Establish in vitro systems for determining nutrient absorption through intestinal mucus ex vivo and the gut epithelium following in vitro digestion using human cell culture models.

(3) Human Metabolic studies to determine the effect of mycoprotein consumption on digestion kinetics and post-prandial endocrine response. Additionally, the impact on the gut microbiome will be assessed as the fermentation products can also regulate the endocrine response and promote gut health.

**Outcome: To demonstrate the impact of manufacturing processes and cooking on the bioaccessibility of nutrients from mycoprotein based products and their influence on digestion of a whole meal. This information will provide structural and functional data for optimising mycoprotein-based foods for optimal health benefits, particularly in obesity, type-2-diabetes and for maintenance of gut health.**

**Representative publications:**

- Mackie A, Goucy S, Rigby N, Moffat J, Capron I, Bajka B. The Fate of cellulose nanocrystal stabilised emulsions after simulated gastrointestinal digestion and exposure to intestinal mucosa. Nanoscale, 2019, 11 (6), 2991-2998
- Edwards CH, Grundy MML, Grassby T, Vasilopoulou D, Frost GS, Butterworth PJ, Berry SEE, Sanderson J, Ellis PR. Manipulation of starch bioaccessibility in wheat endosperm to regulate

starch digestion, postprandial glycemia, insulinemia, and gut hormone responses: A randomized controlled trial in healthy ileostomy participants. American Journal of Clinical Nutrition, 2015, 102 (4), 791-800.

## 3.3 Gestational diabetes and depression: A role for islet serotonin

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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:**

- Drynda, R., Peters, C. J., Jones, P. M. & Bowe, J. E. (2015) The role of non-placental signals in the adaptation of islets to pregnancy. *Hormone and Metabolic Research*. 47; 64-71

- 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

## 4.3 The assessment of lung pathophysiology using a novel and non-invasive pulmonary function test

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**Project description:**

The assessment and management of many respiratory conditions is largely dependent on traditional lung function tests such as spirometry. However, these lung function 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 to perform, which may be difficult/impossible in certain settings such as intensive care. The inspired sinewave technique (IST) is a novel non-invasive technology to measure cardiorespiratory function. This technique is being developed and tested at Kings College London and the University of Oxford as part of collaborative NIHR research grant.

Over the next 3 years we aim to further validate the technology in healthy participants, and compare its performance in assessing different respiratory diseases with traditional lung function tests and chest CT scans. A PhD student would have the opportunity to develop a variety of practical 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 test. The student would also be introduced to skills in the mathematical modelling of physiological systems and the engineering of new hardware and software.

Year 1: Become proficient 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)

## 5.3 Targeting beta-cell iron levels to treat type 2 diabetes

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### Project description:

**Targeting 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 disease mechanisms is crucial for devising 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 shown that excess iron levels, via the actions of a protein called lipocalin-2, play a key role in beta-cell failure in T2D. Additionally, evidence has linked altered iron and lipocalin-2 levels to the anti-diabetic effects of bariatric surgery and the gut microbiota. 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 novel nutritional advice and treatment targets for T2D.

**Skills training:**

Cell culture, islet isolation, insulin secretion radioimmunoassay, 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 islet beta-cell function (insulin secretion) and mass (apoptosis, proliferation and differentiation)

Year 2: Determine the mechanisms of action of lipocalin-2 on □-cell function and mass

Year 3+: Examine the effects of excess iron/lipocalin-2 on beta-cell function in vivo in mice, as well as determining changes in iron/lipocalin-2 in human bariatric surgery patient samples.

### Representative publications:

- Sayers SR, Beavil RL, Fine NHF, Huang GC, Choudhary P, Pacholarz KJ, Barran PE, Butterworth S, Mills CE, Cruickshank JK, Silvestre MP, Poppitt SD, McGill A, Lavery GG, Hodson DJ, Caton PW. Structure-functional changes in eNAMPT at high concentrations mediate mouse and human beta-cell dysfunction in type 2 diabetes. Diabetologia, 2019 (in press)

- 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.

## 6.3 First-in-man arterial oxygen sensing in acute lung injury

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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 excessive or 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 waveforms' 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:**

- Crockett et al. (2019) Tidal changes in $PaO_2$ and their relationship to cyclical lung recruitment/derecruitment in a porcine lung injury model. *British Journal of Anaesthesia* 122(2): 277-285 [**Formenti F** is senior and corresponding author; impact factor 6.2]

- 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 (Impact factor 37.7)

## 7.3 Protecting renal mitochondrial DNA from hyperglycemia induced damage.

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**Project description:**

Diabetic nephropathy (DN) is a major cause of kidney failure in the western world for which there is no treatment apart from renal replacement therapy. Mitochondria are cellular organelles and the site of energy production in the cell which contain their own extranuclear genome (mtDNA). We have shown that mitochondrial dysfunction is involved in the development of DN, specifically we have found that diabetes-induced damage to mtDNA is an early step leading to mitochondrial damage, loss of energy and cellular death.

In the current project the student will:

1. Set up assays that can determine the time course of diabetes-induced damage to cellular mtDNA and mitochondrial function in human renal cells and may include co-culture/ 3D culturing techniques (mesangial, tubular, podocytes) with cells grown in high glucose (25mM) and in physiological glucose conditions (5mM glucose) (Year 1).
2. Undertake screening with selected compounds that can prevent diabetes induced changes to mitochondrial parameters (Year 2 and 3) and determine at what point diabetes induced damage is irreversible.
3. Determine the prevalence and location of mtDNA damage in clinical samples from the KingsDiab cohort (Years 2 and 3).

The techniques involved include mammalian cell culture, DNA, RNA and protein work, including real time qPCR, a range of assays measuring mitochondrial function and next generation sequencing. The student will gain training in a range of cellular biology /molecular biology /translational techniques and join a vibrant research group comprising of postdocs, PIs and PhD students within the Department of Diabetes. Additional opportunities include options to visit expert labs to learn emerging methodology in mitochondrial research within an EU consortium that the primary supervisor is part of.

**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):499-512.

- Taylor, K.M., Hiscox, S., Nicholson, R.I., Hogstrand, C., Kille, P. (2012) Protein Kinase CK2 Triggers Cytosolic Zinc Signaling Pathways by Phosphorylation of Zinc Channel ZIP7. Sci. Signal. 5, ra11.

## 8.3 Are artificial neural networks better than traditional methods in risk prediction for NSAID associated acute kidney injury, AKI and heart failure, HF in individuals with chronic kidney disease?

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**Project description:**

Approximately 60% of patients with chronic kidney disease (CKD), report chronic pain. Non-steroidal anti-inflammatory medications (NSAIDs), are widely prescribed to control joint inflammation and pain. However long term NSAID use is associated with serious ill health including kidney damage (AKI) and heart failure (HF), which may lead to hospitalisation. The aim of this project is to understand who can receive NSAIDs safely, and at what level of reduced kidney function the risk of AKI or HF increases, enabling population stratification for risk.

Machine learning approaches have been successfully used in AKI prediction in hospital (but not population settings) 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 algorithm will select the best model to minimize the loss between the actual result vs. predicted result.

The project will explore differences and commonality between results found using traditional statistical methods and ANN methods to determine whether results are similar and evaluate the robustness of each model using receiver operating characteristic curve (ROC statistic) for sensitivity and specificity of both models in training and validation data cohorts.

Skills training: epidemiological, statistical evidence synthesis and machhine learning approaches, using two large UK population datasets.

Objectives:

Yr1 Systematic review of AKI and HF risks in NSAID exposed patients with CKD.

Yr2 Develop clinical research data sets for analyses.

Yr3 Pilot and validate use of personalised risk prediction for AKI and HF, using traditional and ML methods.

**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.

## 9.3 Neural mechanisms underlying GnRH pulse generation by KNDy neurones

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**Project description:**

The hypothalamic gonadotrophin-releasing hormone (GnRH) pulse generator that drives the pulsatile secretion of the gonadotrophic hormones, LH and FSH, is critical for reproduction. The KNDy neurones (acronym: neurones co-express: Kisspeptin, Neurokinin B and Dynorphin) of the hypothalamus directly stimulate GnRH neurones. It is speculated that the KNDy neuronal network generates oscillations and comprises the GnRH pulse generator. **The most pressing question now is, what initiates and regulates the rhythmic activation of the KNDy neural network to drive pulsatile secretion of GnRH essential for normal ovarian cyclicity and ovulation?**

Combining mathematical modelling with cutting edge in-vivo experimentation, including optogenetics (O'Byrne) and neuropharmacology (Cox) will provide unprecedented access to the function of the KNDy network and understanding of key mechanisms underpinning the activity of the GnRH pulse generator and its modulation by environmental perturbations, including stress.

**Objectives:**

MRes project: Robotic surgery for injection of viral vectors for optogenetics. Experimental approaches for measurement of plasma LH and gene expression (RT-PCR) in brain tissue in stress models.

Year 1 PhD: Determine the optogenetic stimulation parameters of the KNDy network underlying LH pulse frequency, as a proxy for GnRH pulse frequency, across the reproductive cycle and their regulation by gonadal steroids.

Year 2/3 PhD: Functional studies utilizing in-vivo optogenetics, chemogenetics, electrophysiological and neuropharmacological techniques will investigate how the KNDy network integrates different neuropeptides to initiate and modulate the GnRH pulse generator. The modulatory influence of key hypothalamic and limbic brain stress-related neuropeptides (corticotrophin-releasing factor and urocortins) on reproduction and anxiety behaviours will also be examined.

**Representative publications:**

- Voliotis M, Li XF, De Burgh R, Lass G, Lightman SL, O'Byrne KT, Tsaneva-Atanasova K. (2019) Mathematical modelling elucidates core mechanisms underpinning GnRH pulse generation. doi: https://doi.org/10.1101/245548

- Ghamari-Langroudi M, Digby GJ, Sebag JA, Millhauser GL, Palomino R, Matthews R, Gillyard T, Panaro BL, Tough IR, Cox HM, Denton JS, Cone RD. (2015) G-protein-independent coupling of MC4R to Kir7.1 in hypothalamic neurons. Nature. 520(7545):94-8

## 10.3 Predicting spontaneous onset of labour using artificial intelligence.

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**Project description:**

Spontaneous onset of labour (SOL) at term is associated with higher chances of uncomplicated birth outcomes. The rate of interventions and cost of healthcare related to labour and delivery is also lower amongst this group of women. Patient reported outcomes measures of satisfaction are also higher. National reports from the National Maternity and Perinatal Audit (NMPA) has demonstrated a variation in the rates of SOL at term. Multiple national initiatives including the NMPA are focused on reducing the unexpected variations observed in maternity care including SOL.

Improved understanding of factors related to SOL will provide insights on potential mechanisms leading to SOL and inform clinical strategies using artificial intelligence (AI) to reduce the observed national variations in SOL. AI is the broader concept of machines being able to learn from data to provide classifications of patterns and prediction of events.

The aim of this project is to use artificial intelligence to predict spontaneous onset of labour at term amongst women with singleton pregnancies. Thus, in summary, this research will:

- contribute to our understanding of factors related to SOL
- develop and validate a machine learning model to detect significant patterns in the present and predict the future SOL
- facilitate cross-institutional and cross-domain collaboration through publishing AI strategy to the research community

**Representative publications:**

- The DESiGN trial (DEtection of Small for Gestational age Neonate), evaluating the effect of the Growth Assessment Protocol (GAP): study protocol for a randomised controlled trial. Trials. 2019 Mar 4;20(1):154. doi: 10.1186/s13063-019-3242-6.

- Patient-specific prediction of functional recovery after stroke. Int J Stroke. 2017 Jul;12(5):539-548. doi: 10.1177/1747493017706241.

## 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 demonstrated that GPR56 deletion is associated with reduced islet mass and beta-cell number, and this project will build on this to provide supporting data underpinning targeting GPR56 as a novel therapeutic strategy to increase functional beta-cell mass.

**Overarching Objectives and Skills Training:**

This project has 4 main objectives

1. Track GPR56 trafficking in beta-cells to define whether classical receptor-specific GPCR desensitisation and internalisation occur after ligand binding (cell culture, transient transfection with SNAP-tag plasmids, fluorescent IHC and confocal microscopy).
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).
3. Identify the effects of the GPR56 peptide agonist TYFAVLM on mouse and human islet function (islet isolation, gene expression quantification, insulin secretion, BrdU incorporation and caspase assays).
4. Determine the requirement of GPR56 for normal glucose homeostasis (GTTs, ITTs and plasma insulin quantification in GPR56 KO mice fed normal chow and high fat diet, pancreas and islet histology, immunoassay).

**Representative publications:**

- Olaniru OE and Persaud SJ (2019) Adhesion G-protein-coupled receptors: implications for metabolic function. Pharmacology & Therapeutics. 198, 123-134

- 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

## 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.

**Representative publications:**

- Connolly B, Maddocks M, MacBean V, Bernal W, Hart N, Hopkins P & Rafferty GF. (2018). Non-volitional assessment of tibialis anterior force and architecture during critical illness. Muscle Nerve 57 (6), 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.
  **Joint Senior Authorship: Harridge-Hart-Montgomery**

## 13.3 Exploring mechanisms and novel treatment strategies for age-associated cardiovascular disease

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**Project description:**

Ageing is the strongest risk factor for cardiovascular (CV) disease and maintenance of tissue health is key to combating age related decline. Two major age-related pathologies are vascular calcification and dilated cardiomyopathy (DCM), which drive vascular stiffening and heart failure. CV ageing mimics, in part, the premature ageing observed in patients with diseases known as laminopathies which are caused by defects in the nuclear lamina and the LINC complex, which mechanically couples the nucleus to the cytoskeleton. Nuclear lamina defects drive CV ageing by accelerating DNA damage and senescence, inducing changes in the epigenome and deregulating mechanical signalling. The aim of this project will be to use in vitro techniques in combination with novel animal models of CV ageing due to nuclear lamina disruption to define temporal mechanisms of ageing and test novel drugs targeting key pathways to extend health span. (Year 1): Investigate the mechanisms that drive nuclear lamina dysfunction during ageing using primary human cells in vitro (Year 2): Physiological and histological phenotyping of 2 novel animal models of CV ageing including analysis of ECM, epigenome and DNA damage/senescence. (Years 2 and 3). Testing of drugs that target pathways identified as key to CV ageing in the animal models to define mechanisms leading to extended healthspan (candidate drugs targeting epigenetic regulators and the DNA damage response have already been identified). 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, blood pressure measurement and histology/immunohistochemistry.

**Representative publications:**

- Prelamin A accelerates vascular calcification via activation of the DNA damage response and senescence-associated secretory phenotype in vascular smooth muscle cells. Liu Y, Drozdov I, Shroff R, Beltran LE, Shanahan CM. Circ Res. 2013 May 10;112(10):e99-109.

- Novel nesprin-1 mutations associated with dilated cardiomyopathy cause nuclear envelope disruption and defects in myogenesis. Zhou C, Li C, Zhou B, Sun H, Koullourou V, Holt I, Puckelwartz MJ, Warren DT, Hayward R, Lin Z, Zhang L, Morris GE, McNally EM, Shackleton S, Rao L, Shanahan CM, Zhang Q. Hum Mol Genet. 2017 Jun 15;26(12):2258-2276.

## 14.3 Understanding molecule delivery across the blood-brain barrier to improve safety of anti-psychotic drugs in elderly patients.

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**Project description:**

Psychotropic drug prescribing is highly prevalent (>50%) in those aged over 65 years, and is associated with significant morbidity, including sedation, postural hypotension, and fall-related injuries, which have a significant impact on quality of life. Those aged over 80 years and/or with a diagnosis of dementia are at greatest risk of side effects, particularly in relation to antipsychotic drugs, whose use is restricted due to an increased incidence of parkinsonism, stroke and death. The underpinning mechanisms of this heightened drug sensitivity are poorly understood, however, research by our group suggest that changes in drug transport across the blood-brain barrier (BBB) may be an important contributor (Sekhar et al., 2019).

This project explores the hypothesis that alterations in transporter activity at the BBB is responsible for the heightened sensitivity to drugs and dose adjustments needed in older patients. This will be addressed using the antipsychotics, risperidone and 9-hydroxyrisperidone, which are commonly used in older people with mental health symptoms, including those with schizophrenia, AD and Parkinson's disease related dementia.

The student will explore the ability of both drugs to cross the BBB using complex and simple transporter models.

Years 1-2: Supervised by Dr Thomas: Complex in vitro BBB models including MDCK-MDR, hCMECD3 and/or bEnd3 cell culture.

Year 2-4: Supervised by Dr Corpe. Candidate transporters identified in years 1-2 will be injected into xenopus laevis oocytes and their drug transport properties studied in isolation.

**Representative publications:**

- Sekhar G.N., Fleckney A., Boyanova S.T., Rupawala H., Lo R., Wang H., Farag D.B., Rahman K.M., Broadstock M., Reeves S., and Thomas S.A. (2019) Region-specific blood-brain barrier transporter changes leads to increased sensitivity to amisulpride in Alzheimer's disease. BIORXIV/2019/582387. https://doi.org/10.1101/582387.

- Corpe CP, Eck P, Wang J, Al-Hasani H, Levine M Intestinal dehydroascorbic acid (DHA) transport mediated by the facilitative sugar transporters, GLUT2 and GLUT8. J Biol Chem. 2013 Mar 29;288(13):9092-101. doi: 10.1074/jbc.M112.436790.