

Theme 3

Physiological

Medicine



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 DTP 2015_Theme3**

Application Deadline: Sunday 11th December 23:59

Shortlisted candidates will be contacted in mid-January and invited to an interview on one of the two dates in February.

Interviews: 6th & 7th February 2017

The 2017/18 studentships will commence in September 2017.

For further information or queries relating to the application process please contact

mrc-dtp@kcl.ac.uk

1.3 Electrical Stimulation of the Upper Airway Dilator Muscles in Obstructive Sleep Apnoea

Co-Supervisor 1: Joerg Steier
Research Division or CAG: AALB
E-mail: Joerg.steier@kcl.ac.uk
Website: <https://kclpure.kcl.ac.uk/portal/joerg.steier.html>

Co-Supervisor 2: Gerrard F Rafferty
Research Division or CAG: AALB
Email: Gerrard.rafferty@kcl.ac.uk
Website: <https://kclpure.kcl.ac.uk/portal/gerrard.rafferty.html>

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 noninvasive electrical stimulation of the upper airway dilator muscles. Both methods seem to achieve a similar effect size in selected patients, potentially improving long-term health outcomes.

Skills training: diagnosis/treatment of sleep disorders; 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 non-invasive electrical stimulation of the upper airway dilator muscles 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,
2. Phenotype characterization of responders and non-responders, functional determinants of response,
3. Feasibility study using transcutaneous electrical stimulation,
4. Preparation of a definitive multi-centre trial in the community.

Patients who currently fail CPAP therapy could benefit from this novel therapeutic approach within 5 years.

Two representative publications:

1. Pengo MF, Xiao S, Ratneswaran C, Reed K, Shah N, Tao Chen,⁵ Abdel Douiri,⁵ Nicholas Hart,^{1,2} Yuanming Luo,³ Gerrard F Rafferty,¹ Gian Paolo Rossi,³ Adrian Williams,^{1,2} Michael I Polkey,⁶ John Moxham,¹ Joerg Steier,^{1,2} Randomised sham-controlled trial of transcutaneous electrical stimulation in obstructive sleep apnoea. *Thorax* 2016; doi:10.1136/thoraxjnl-2016-208691
2. Steier J, Seymour J, Rafferty GF, Jolley CE, Solomon E, Luo YM, Man WDC, Polkey MI, Moxham J. Continuous transcutaneous submental electrical stimulation in obstructive sleep apnea: a feasibility study. *Chest* 2011;140:998–1007.

3.3 Protective role of CGRP in cardiovascular disease

Co-Supervisor 1: Susan D Brain

Research Division or CAG: Cardiovascular

E-mail: sue.brain@kcl.ac.uk

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

Co-Supervisor 2: Manasi Nandi

Research Division or CAG: Institute of Pharmaceutical Science

Email: Manasi.nandi@kcl.ac.uk

Website: <http://www.kcl.ac.uk/lsm/research/divisions/ips/research/pharmathera/Staff/Nandi.aspx>

Name of Collaborating Clinician: Prof Philip Chowienczyk

Research Division or CAG: Cardiovascular

Email: phil.chowienczyk@kcl.ac.uk

Website: <https://kclpure.kcl.ac.uk/portal/phil.chowienczyk.htm>

Project description:

Cardiovascular disease is a major disease problem and can prove fatal. Whilst treatments are available, the mortality rates, remain high at 27% (BHF Cardiovascular Disease Statistics 2015). This project will study the role of the vasodilator calcitonin gene-related peptide (CGRP). This peptide is released from sensory nerves that surround blood vessels. This group has evidence that it can protect the blood vessels and heart from the damage which occurs in cardiovascular disease and also in response to environmental stresses such as the cold.

We have recent evidence, that CGRP has a protective role in mice models of hypertension, cold-induced injury and heart failure by inhibiting and also reversing the damage to blood vessels. We now want to determine the importance and the mechanisms involved in the activity of the native peptide and also of a newly developed stabilised analogue which has a substantially longer half-life.

The PhD student will work with a translational team studying the mechanisms of CGRP action using both mouse models of disease and also with mechanistic investigations in human volunteers. Prof Brain has expertise in sensory nerves and CGRP and their role in the periphery, especially mouse and human skin. Dr Nandi is an expert in the study of cardiovascular regulation using radio-telemetry and it's advanced analysis.

This research may lead to novel preventive and therapeutic treatments for patients that suffer a loss of CGRP, which occurs in conditions associated with a high risk of cardiovascular disease.

Two representative publications:

1. Smillie SJ, King R, Kodji X, Outzen E, Pozsgai G, Fernandes E, Marshall N, de Winter P, Heads RJ, Dessapt-Baradez C, Gnudi L, Sams A, Shah AM, Siow RC, Brain SD. An ongoing role of α -calcitonin gene-related peptide as part of a protective network against hypertension, vascular hypertrophy, and oxidative stress. *Hypertension*. 2014 63:1056-62.
2. Sand CA, Starr A, Wilder CD, Rudyk O, Spina D, Thiemermann C, Treacher DF, Nandi M. Quantification of microcirculatory blood flow: a sensitive and clinically relevant prognostic marker in murine models of sepsis. *J Appl Physiol*. 2015 118:344-54.

4.3 Innate immune host defense and microbiome interactions in the pregnant female reproductive tract

Co-Supervisor 1: Dr Rachel M. Tribe

Research Division or CAG: Women's Health

E-mail: rachel.tribe@kcl.ac.uk

Website: <http://www.kcl.ac.uk/lsm/research/divisions/wh/groups/pregnancy/index.aspx>

Co-Supervisor 2: Dr A. James Mason

Research Division or CAG: Institute of Pharmaceutical Science

Email: james.mason@kcl.ac.uk

Website: <http://www.kcl.ac.uk/lsm/research/divisions/ips/research/pharmabio/Staff/Mason/index.aspx>

Name of Collaborating Clinician: Prof. Andrew Shennan

Research Division or CAG: Women's Health

Email: andrew.shennan@kcl.ac.uk

Website: <https://kclpure.kcl.ac.uk/portal/en/persons/andrew-shennan.html>

Project description:

This project will provide a mechanistic understanding and suggest interventions to overcome the global problem of spontaneous preterm birth (sPTB). It expands upon our discovery that cervico-vaginal concentrations of certain host defense peptides predict cervical shortening and risk of sPTB; investigating how changes in HDP expression are linked to the presence of different vaginal bacteria and, in turn, identifying changes in metabolites capable of triggering a pro-inflammatory response. Consequently the project will differentiate cause and effect leading to improved diagnostics and interventions. The project utilizes samples/metadata from our NIHR funded INSIGHT study of 2000 pregnancies.

Year 1. Determine how vaginal pH and other stimuli influence production of HDPs by vaginal epithelial cells. Understand the host cell response to different community states. Techniques: established cell lines and primary cell culture, qPCR, western blot, ELISA, and pharmacological characterization of signaling pathways, RNAseq.
Year 2-3. Determine how candidate bacteria (identified from ongoing human studies) influence the vaginal environment (nutrient and pH) and HDP function (cell based assays, microbiological assays, NMR metabolomics).

Year 3-4. Determine the impact of pH on HDPs actions against bacteria associated with vaginal dysbiosis in pregnancy (microbiome profiling using 16S Illumina MiSeq; microbiological and biophysical assays)

The project has flexibility to focus more on molecular biology techniques, metagenomic/metabolomic or membrane biophysics approaches depending on candidate interest/skill set. Training will be provided in both supervisors' well-equipped research facilities/laboratories. The student will have access to KCL core and BRC facilities, relevant personal development training, and journal clubs and seminars.

Two representative publications:

1. Abbott DA, Chin Smith EC, Seed PT, Chandiramani M, Shennan AH, Tribe RM. Raised trappin2/elafin protein in cervico-vaginal fluid is a potential predictor of cervical shortening and spontaneous preterm birth. PLoS One, 2014; 9:e100771.

2. Kozłowska J, Vermeer LS, Rogers GB, Rehnuma N, Amos S-BTA, Koller G, McArthur M, Bruce KD, Mason AJ.* Combined systems approaches reveal highly plastic responses to antimicrobial peptide challenge in Escherichia coli. PLoS Pathogens 2014 (10) e1004104

5.3 The influence of industrial interesterification of dietary fats on postprandial lipid metabolism and subsequent cardio-metabolic health effects.

Co-Supervisor 1: Dr Wendy Hall

Research Division or CAG: Diabetes and Nutritional Sciences

Email: wendy.hall@kcl.ac.uk

Website: <https://kclpure.kcl.ac.uk/portal/wendy.hall.html>

Co-Supervisor 2: Dr Sarah Berry

Research Division or CAG: Diabetes and Nutritional Sciences

E-mail: sarah.e.berry@kcl.ac.uk

Website: <http://kclpure.kcl.ac.uk/portal/sarah.e.berry.html>

Project description:

Scientific basis: Interesterification of fats, where fatty acids are rearranged on the glycerol backbone of triacylglycerols, is extensively used by the food industry to create fats with desirable functional characteristics for applications in spreads and bakery products, negating the need for harmful trans fatty acids. The effects of commonly consumed interesterified fats on postprandial lipaemia, an independent risk factor for cardiovascular disease, are unknown. This research aims to investigate the effect of interesterified palm oil-based fats on postprandial lipid metabolism and subsequent cardio-metabolic health effects in a series of human metabolic feeding studies at Kings College London. The mechanisms underpinning proposed differences in the postprandial gastrointestinal handling and metabolism of these interesterified fats will be studied using specialist stable isotope techniques at University College London.

Objectives: Human Study 1 (year 1-2/3) will test the hypothesis that interesterified palm oil blends elicit differences in postprandial lipaemia in healthy participants compared with non-interesterified equivalents due to differences in rates of digestion and metabolism.

Human Study 2 (Year 2-3/4) will test the hypothesis that IE fats differentially influence acute changes in markers of cardiovascular health compared with a control fat.

Mechanisms underpinning differential postprandial responses will be studied using stable isotope techniques to determine effects on lipid absorption, oxidation and metabolism.

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 stable isotope techniques (IRMS).

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.

6.3 Role of soluble Nogo-B as a modulator of vascular health in patients with diabetes and chronic vascular complications.

Co-Supervisor 1: Prof Luigi Gnudi (Clinical academic)

Research Division or CAG: Cardiovascular

E-mail: luigi.gnudi@kcl.ac.uk

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

Co-Supervisor 2: Prof Giovanni Mann

Research Division or CAG: Cardiovascular

Email: Giovanni.mann@kcl.ac.uk

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

Project description:

Endothelial dysfunction (ED) drives diabetic vascular complications. Chronic metabolic overload (e.g. diabetes) stimulates mitochondrial superoxide production, which leads to endoplasmic reticulum (ER)- stress and protracted activation of unfolded protein response (UPR), resulting in endothelial cells (ECs) apoptosis, inflammation and ED.

High levels of Neurite-Outgrowth-Inhibitor (Nogo)-B, localised in the ER, have been proposed to reduce ER-mitochondria interaction, resulting in attenuation of oxidative stress and favouring cell survival. Nogo-B is downregulated in ECs in diabetes, an event prevented by soluble Nogo-B (sNogo-B), a Nogo-B circulating isoform. Nogo-B is reduced in atherosclerotic vessels in humans and is implicated in vascular remodelling.

We hypothesise that uncoupling mitochondrial-ER interactions (via Nogo-B upregulation) may exert a protective effect on ED in diabetes.

Experiments will be conducted with ECs (wild/Nogo-B knockout cells) in vitro, adapted to physiological oxygen (5%O₂) as encountered in vivo.

Objectives: To investigate:

1. The effect of high-glucose on Nogo-B expression and mitochondria superoxide production/ER- stress/UPR, and whether this can be ameliorated by Nogo-B overexpression;
2. The putative protective role of sNogo-B and its mechanism/s (Nogo-B upregulation, binding to NgBR receptor/signalling, etc.);
3. The spatial relationship ER conditions of high/low Nogo-B cellular levels;
4. The potential correlation of ED, assessed with flow-mediated dilation, with circulating sNogo-B levels in the general and diabetic population.

The candidate will be co-supervised by a clinician and basic scientists with established expertise in diabetic vascular disease; the student will acquire advanced techniques on cell culture (using an O₂- regulated SCI-tive workstation), on cell signalling/imaging, DNA-cloning, and clinical research.

Two representative publications:

1. 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 glomerularangiopoietin-1 therapy forearly diabetickidney disease. J Am Soc Nephrol. 2014, 25(1):33-42.
2. 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 Radic Biol Med. 2015 92:152-62.

Project submission form:

7.3 The role of mitochondrial DNA damage in the development and progression of diabetic retinopathy

Co-Supervisor 1: Dr Afshan Malik

Research Division or CAG: DNS

E-mail: afshan.malik@kcl.ac.uk

Website: <http://www.kcl.ac.uk/lsm/research/divisions/dns/about/people/Profiles/afshanmalik.aspx>

Co-Supervisor 2: Professor Sobha Sivaprasad

Research Division : Honorary Reader, DNS, KCL

Email: senswathi@aol.com

Website: <http://www.ucl.ac.uk/loo/>

Project description:

The role of mitochondrial DNA mutations and inflammation in adult blindness caused by diabetic retinopathy Diabetic retinopathy (DR), a major cause of blindness, affects >30million diabetes patients worldwide and remains a major cause of visual impairment in the working-age population for which there is no treatment. Mitochondria are cellular organelles and the site of energy production in the cell. Despite increasing evidence of mitochondrial dysfunction being involved in the development of DR, until recently there were no clinical human studies supporting this view. We recently published the first human study showing that MtDNA changes can be detected in blood samples from DR patients and have found, using patient blood samples and animal/cell models, that diabetes can lead to elevated circulating MtDNA. As MtDNA resembles bacterial DNA it may elicit an inflammatory response via activation of the TLR9 pathway and activate inflammasomes. Recently we have discovered novel MtDNA mutations and deletions in DR patients which have previously never been reported. In the current project the student will (a) test the novel hypothesis that the damaged MtDNA is causative of energy deficit in the retina and chronic inflammation in circulation (b) characterise the time course of mitochondrial changes associated with DR using in-vitro models and (c) Identify and test therapeutic and preventative strategies. For the rotation/year 1, the student will use human patient samples to define the incidence of MtDNA mutations in DR. These studies will be expanded further and ARPE 19 cells will be used to mimic the damage seen in the retina in hyperglycemic conditions in order to characterise the mitochondrial changes and then test a range of therapeutic strategies. The student will gain training in a range of cell biology and molecular biology techniques including tissue culture, DNA/RNA work, real time quantitative PCR, functional assays and bioenergetics and will join a vibrant research facility (The diabetes research group) based at the Guys campus.

Two representative publications:

1. Malik, Parsade, Ajaz, Crosby-Nwaobi, Gnudi, Czajka , Sivaprasad (2015) Altered circulating mitochondrial DNA and increased inflammation in patients with diabetic retinopathy. *Diabetes Res Clin Pract.* 2015 Dec;110(3):257-65. doi: 10.1016.
2. Czajka, Ajaz, Gnudi, Parsade, Jones, Reid, Malik (2015) Altered mitochondrial function, mitochondrial DNA and reduced metabolic flexibility in patients with diabetic nephropathy, *eBiomedicine*, Apr 11;2(6):499-512.

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

Co-Supervisor 1: Dr. Els Henckaerts

Research Division or CAG: DIIID

E-mail: els.henckaerts@kcl.ac.uk

Website:

<http://www.kcl.ac.uk/lsm/research/divisions/diiid/departments/infectious/research/henckaerts/index.aspx>

Co-Supervisor 2: Prof. Ajay Shah

Research Division or CAG: Cardiovascular Division

Email: ajay.shah@kcl.ac.uk

Website: <http://www.kcl.ac.uk/lsm/research/divisions/cardio/index.aspx>

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 from 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 eIF2 α -mediated stress signaling. *EMBO J.* 2016;35:319–334.

2. Identification of a Functionally Relevant Adeno-Associated Virus Rep68 Oligomeric Interface. Bardelli M, Zárte-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.

9.3 The role of progesterone metabolites in susceptibility to gestational diabetes mellitus

Co-Supervisor 1: Catherine Williamson

Research Division or CAG: Women's Health

E-mail: catherine.williamson@kcl.ac.uk

Website: <https://kclpure.kcl.ac.uk/portal/catherine.williamson.html>

Co-Supervisor 2: James Bowe

Research Division or CAG: Diabetes and Nutritional Sciences

Email: james.bowe@kcl.ac.uk

Website: <http://www.kcl.ac.uk/lsm/research/divisions/dns/about/people/Profiles/jamesbowe.aspx>

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 the first 1-2 years the student will use archived samples from human in vivo studies (timed blood sample collection following standardised meals and parallel evaluation of the gut microbiome and metabolites), and further investigate mechanisms by which progesterone and its metabolites influence gut hormone release using human intestinal explants and the NCI-H716 cell line. In parallel the student will study the impact of endocrine signals on glucose metabolism in two murine models of gestational diabetes mellitus (db/+ and high fat diet-fed mice). In the final two years the student will evaluate drugs (FXR and TGR5 ligands) that impact enteroendocrine cell/islet function with the aim of preventing/delaying onset of gestational diabetes.

Two representative publications:

1. Martineau MG, Raker C, Dixon PH, Chambers J, Machirori M, King NM, Hooks ML, Manoharan R, Chen K, Powrie R, Williamson C. The Metabolic Profile of Intrahepatic Cholestasis of Pregnancy is Associated with Impaired Glucose Tolerance, Dyslipidemia, and Increased Fetal Growth. *Diabetes Care* 2015;38:243-248 PMID: 25504029
2. Abu-Hayyeh S, Ovadia C, Lieu TM, Jensen D, Chambers J, Dixon PH, Lövgren-Sandblom A, Bolier R, Tolenaars D, Kremer A, Syngelaki A, Noori M, Williams D, Marin JJ, Monte MJ, Nicolaidis KH, Beuers U, Oude-Elferink R, Seed PT, Chappell L, Marschall HU, Bunnett NW, Williamson C. Prognostic and Mechanistic Potential of Progesterone Sulfates in Intrahepatic Cholestasis of Pregnancy and Pruritus Gravidarum. *Hepatology* 2016; 63: 1287-1298 PMID: 26426865

10.3 Strategies to improve islet transplantation outcomes

Co-Supervisor 1: Aileen King

Research Division or CAG: Diabetes and Nutritional Sciences

E-mail: aileen.king@kcl.ac.uk

Website: <http://www.kcl.ac.uk/lsm/research/divisions/dns/about/people/Profiles/aileenking.aspx>

Co-Supervisor 2: Pratik Choudhary

Research Division or CAG: Diabetes, Endocrinology, Nutrition, Obesity, Vision and Related Surgeries Clinical Academic Group

Email: pratik.choudhary@kcl.ac.uk

Website: <http://www.kcl.ac.uk/lsm/research/divisions/dns/about/people/Profiles/pratikchoudhary.aspx>

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. 2016. DOI: 10.3727/096368916X692258
2. Evidence-informed clinical practice recommendations for treatment of type 1 diabetes complicated by problematic hypoglycemia. Choudhary P, Rickels MR, Senior PA, Vantighem MC, Maffi P, Kay TW, Keymeulen B, Inagaki N, Saudek F, Lehmann R1, Hering BJ. Diabetes Care. 2015 Jun;38(6):1016-29.

11.3 Characterizing platelet purinergic receptor activity as a therapeutic target in critically ill patients with systemic inflammation and sepsis.

Co-Supervisor 1: Dr Simon Pitchford

Research Division or CAG: Institute of Pharmaceutical Science

E-mail: simon.pitchford@kcl.ac.uk

Website: <http://www.kcl.ac.uk/biohealth/research/divisions/ips/research/pharmathera/Staff/Pitchford.aspx>

Co-Supervisor 2: Professor Clive Page

Research Division or CAG: Institute of Pharmaceutical Science

Email: clive.page@kcl.ac.uk

Website: <http://www.kcl.ac.uk/biohealth/research/divisions/ips/research/pharmathera/Staff/Page.aspx>

Name of Collaborating Clinician: Dr Manu Shankar-Hari

Research Division or CAG: Intensive Care Medicine; Guy's and St Thomas' NHS Foundation Trust. Immunology, Infection & Inflammatory Disease Research Division

Email: manu.shankar-hari@kcl.ac.uk

Website: <http://www.guysandstthomas.nhs.uk/our-services/consultant-profiles/critical-care/manu-shankar-hari.aspx>

Project description:

Scientific basis: We have identified that the platelet P2Y1 receptor is necessary for important inflammatory processes that occur in both septic and allergic pulmonary inflammation, a phenomenon that is very different to P2Y1 mediated platelet activity leading to aggregation (haemostasis). This 'dichotomy in platelet activity' arising from P2Y1 stimulation may be explained by the induction of selective signalling pathways (Rho kinase, and Rac kinase) by the inflammatory milieu that are otherwise redundant during platelet aggregation (haemostasis). Having access to blood samples from critically ill patients with inflammation arising from sepsis and Adult Respiratory Distress Syndrome (ARDS) will allow this project to characterise P2Y1 signalling and activation of platelets and profile the suitability of P2Y1 as a therapeutic target.

Skills training will involve isolation of platelet and leukocyte populations to enable phenotypic analysis (flow cytometry, Western blotting, protein arrays); haematological and immunological based in vitro functional assays (platelet aggregation, adhesion molecule expression, platelet and neutrophil chemotaxis); comparing platelets from healthy vs sepsis/ARDS patients. Simple in vivo pulmonary inflammation and haemostasis assays can be used under supervision of Dr Simon Pitchford.

Objectives:

Year 1: Analysis of platelet phenotype. Investigate P2Y1 expression, signalling and abundance of ADP and other P2Y1 ligands from patient blood.

Year 2: Explore functional dichotomy. Use of haematological and immunological assays.

Year 3: Pharmacological characterisation. Investigate influence of distinct (orthosteric vs allosteric) P2Y1 binding sites.

Year 4: Determine physiological relevance. Use in vivo assays to measure influence of distinct P2Y1 ligands, orthosteric and allosteric antagonists.

Two representative publications:

1. Amison RT, et al. RhoA signaling through platelet P2Y(1) receptor controls leukocyte recruitment in allergic mice. *J Allergy Clin Immunol.* 2015; 135:528–538

2. Pan D, et al. P-Rex and Vav Rac-GEFs in platelets control leukocyte recruitment to sites of inflammation. *Blood.* 2015; 125: 1146–1158