Cardiometabolic Early Career Researchers' Event: Encouraging Collaboration and Connectivity

Thursday, 2nd November 2017
McGrath Centre, St Catharine's College, Cambridge

#CMECR17

Organized by the Cambridge Cardiovascular Strategic Research Initiative, and the Cambridge Metabolic Network Joint Organizing Committee

Programme

08:30-09:00 Registration

09:00-09:15 Professor Toni Vidal-Puig: *Welcome & Introduction to the HLRI*

Session 1: Developmental programming of cardiometabolic disease

09:15-09:45 Professor Sue Ozanne: *Programming by maternal overnutrition: A developing obesity crisis*

09:45-09:55 H Yong: *IGF2 deletion from the placental endocrine layer alters maternal sensitivity to glucose and insulin, and affects fetal and early postnatal growth in mice*

09:55-10:05 R Hess: *What's that smell? First evidence of cardio-protective actions of hydrogen sulphide in the developing heart*

10:05-10:15 AM Spiroski: *Sex-specific programming of cardiac bioenergetics by chronic hypoxic pregnancy and mitochondria-targeted antioxidant therapy*

10:20-11:35 Connections session: *Identifying links between research areas*

Session 2: Translational science: From bench to bedside

11:35-12:05 Dr Magnus Althage: *From bench to bedside through translatable in vitro models*

12:05-12:35 Dr Duncan Richards: *Anti-SAP treatment for systemic amyloidosis; the value of mechanistic models*

12:35-13:10 Techniques session: A chance to find others with similar interests

13:10-14:20 Lunch & Posters

Session 3: Inflammation and platelet function in cardiometabolic disease

14:20-14:50 Professor Khalid Naseem: *New models of Platelet Hyperactivity - the Proinflammatory Platelet.*

14:50-15:00 M Nus: *Marginal zone B cells limit TFH differentiation in atherosclerosis in response to a high cholesterol diet*

15:00-15:10 V Azzu: *Is de novo lipogenesis a drive of fibrosis in non-alcoholic fatty liver disease?*

15:10-15:20 S Burgess: *Inhibiting TMEM16F, a platelet scramblase*

15:25-15:40 Tea & Coffee

Session 4: Mechanisms of obesity and its cardiometabolic effects

15:40-16:10 Professor Sir Stephen O'Rahilly: *Some observations on the causes and consequence of obesity*

16:10-16:20 J Beeson: *Effect of maternal exercise during obese pregnancy on the cardiovascular health of male mouse offspring*

16:20-16:30 G Bidault: *SREBP1c mediated de novo lipogenesis sequesters NADPH to inactivate macrophages antioxidant defences and promote their alternative activation*

16:30-16:40 V Auyeung: *Investigating the aetiologic links between the gut microbiota, metabolic profiles and metabolic disease*

16:45-17:00 Professor Toni Vidal-Puig: *Prizes & closing remarks*

17:00-18:00 Drinks and Networking

Welcome from the Organising Committee

Welcome to the Cardiometabolic Early Career Researchers' Event! This event supports integrative cardiometabolic science, and showcases collaboration and connectivity across major research themes. The Cambridge Cardiovascular Strategic Research Initiative and Cambridge Metabolic Network joint organising committee have built a day around you, the Early Career Researcher (ECR).

The joint organising committee, a team of eight ECRs, together with network coordinators, Katja and Jane, and the support of Vicky, have developed an exciting programme. Throughout the day you will hear from world leaders in cardiometabolic science from within the University of Cambridge, the University of Leeds, and industry partners AstraZeneca and GlaxoSmithKline, and you will see the exciting research happening across the themes from University of Cambridge ECRs. We also outline plans for the Heart and Lung Research Institute (HLRI), expected to open 2021, which allows expansion of basic and clinical research capabilities, bringing together researchers from across Cambridge.

We have Sarah Cruise, a professional facilitator from Eloquential, to help facilitate networking, and we are using blendology™ badges. These badges will provide you with the contact details of everyone you have connected with during the event! There are also special technique-focused sessions that provide you the opportunity to link up with other ECRs with similar interests across the University, and from our industry partners. We hope you take this opportunity to build new relationships and possibly establish future collaborations!

We hope you enjoy the day!

Ana-Mishel Spiroski Annabel Taylor Caroline Archer Hannah Yong

Jane Sugars Jessica Walsh Katja Kivinen

Sarah Burgess Tessa Cacciottolo Victoria Auyeung Vicky Reid

Cambridge Heart & Lung Research Institute

The University of Cambridge is raising funds to build a dedicated Heart & Lung Research Institute (HLRI) on the Cambridge Biomedical Campus. This initiative has been catalysed by the relocation of Papworth Hospital and the transfer of AstraZeneca R&D facilities to Cambridge in 2018. If the fundraising is successful, we expect that the building work will start by 2019 and the HLRI will open in 2021.

The HLRI will bring together clinical expertise in cardiovascular and respiratory disease from its NHS partners and cutting-edge science from the University of Cambridge, together with industry know-how to identify tractable drug targets and the production of high quality molecules against such targets.

The HLRI will include a designated clinical research facility with the capability to perform first-into-patient clinical trials. Additionally, the HLRI will provide core cell phenotyping, histopathology, immunostaining, FACS, and confocal microscopy facilities.

Prof Nicholas Morrell acts as the HLRI Interim Director and is supported by the leaders of the six research themes: Cardiometabolism & Inflammation (Prof Antonio-Vidal Puig); Cardiovascular Biology (Prof Martin Bennett); Experimental Medicine & Therapeutics (Prof Ian Wilkinson); Functional Genomics (Prof Willem Ouwehand); Population Sciences (Prof John Danesh); Respiratory Biology (Prof Edwin Chilvers).

The Cardiometabolism & Inflammation theme will focus on identifying pathogenic mechanisms linking obesity, diabetes and cardiometabolic complications that can be used for therapeutic approaches and/or diagnostic, prognostic or therapeutic biomarkers. The research strategy will combine a hypothesis driven approach and a non-biased systems approach using integration of multiple -omics and other computational data obtained from murine models, human iPSCs, and human epidemiology studies.

Cardiovascular Strategic Research Initiative

The Strategic Research Initiative coordinates cardiovascular and related research in Cambridge. We connect researchers across the University of Cambridge and affiliated research institutes, hospitals, and industry partners. Our aim is to become one of the world's leading hubs for basic and clinical cardiovascular research within the next 10 years. We work closely with two British Heart Foundation -funded research centres to maximise the potential for interdisciplinary funding and positions for students and staff, and are strengthening our strategic links with world-leading cardiovascular centres in the USA, Europe, and Asia. Our research objectives cut across five main themes that represent our strengths: Cardiovascular Biology, Cardio-Metabolism, Experimental Medicine & Therapeutics, Functional Genomics, and Population Sciences.

Cambridge Metabolic Network

The Cambridge Metabolic Network links and promotes research activities among the broad academic research community in Cambridge, welcoming members of all six Schools of the University and colleagues from key regional partner organisations. Our goal is to generate fresh insight into research in the field of metabolism. We want to establish a multidisciplinary community of researchers, support development of new research, co-ordinate activities in areas of importance to research in metabolism and facilitate translation of research to benefit current and future populations.

Interactive Badges

This event uses interactive badges to help facilitate networking by providing you with the contact details for people that you meet during the event!

How do they work?

Collect your badge from the welcome desk on arrival. Tap your badge with everyone that you meet during the event to make a connection. After the event you will be able to view the contact details of everyone you've connected with.

How do I see my connections?

Signup details for your account have been emailed to the email address with which you registered for the event. Once you have created a password, you will be able to login and view your connections from the event.

Happy tapping!

blendology

Welcome and Closing Remarks

Professor Toni Vidal-Puig

Associate Director, MRC Metabolic

Disease Unit, University of Cambridge

My team explores the molecular mechanisms involved in controlling energy expenditure, fat deposition, and the mechanisms controlling the partition of energy towards oxidation or storage.

Specifically we are interested in the following interrelated questions.

1. How the expansion of adipose tissue typically associated with obesity relates to the development of the Metabolic Syndrome. More specifically we are exploring whether **lipotoxicity** and/or changes in adipokines secreted by adipose tissue affect insulin sensitivity in other organs (skeletal muscle, heart, liver, brain, beta cells and macrophages).
2. Whether modifications in **adipogenesis** and remodeling of adipose tissue may be good strategies to ameliorate the metabolic effects associated with obesity.
3. The molecular mechanisms that control **energy expenditure** and brown fat activation.
4. Whether modulation of **partitioning of nutrients** towards fatty acid oxidation in skeletal muscle and away from storage in adipose tissue may prevent the devastating metabolic effects of obesity.

To address these challenges is a daunting task that requires the modulation of highly integrated and complex mechanisms of energy homeostasis designed to prevent negative energy balances. According to this integrated concept of energy homeostasis, my laboratory is using an **Integrated Physiology** approach that relies greatly upon the generation and detailed *in vivo* phenotyping of genetically modified organisms. This is used together with **Systems Biology** approach integrating transcriptomic and lipidomic analysis, using bioinformatics to identify organ specific lipid metabolic networks relevant for insulin resistance and metabolic disease.

Keynote Speakers

Professor Sir Stephen O'Rahilly

Director, MRC Metabolic Disease Unit.

Director, Metabolic Research Laboratories.

Co-Director, Institute of Metabolic Sciences,

University of Cambridge.

Keynote: *Some observations on the cause and consequences of obesity*

I am interested in the aetiology and pathophysiology of human metabolic and endocrine disease and how such information might be used to improve in the diagnosis, therapy and prevention of these diseases. One major area of continuing interest is to better understand why some people are very susceptible to obesity and others seem resistant. We can learn quite a bit about this from human genetics but those discoveries need to be better integrated with growing fundamental knowledge regarding processes controlling energy intake and expenditure. I am also very interested in why people, particularly those who become obese, become resistant to the glucose lowering effects of the hormone insulin. Again the integration of human genetics with basic studies in cells and disease models will be necessary to advance our understanding. I am lucky to work in an environment where I can collaborate freely with a wide range of Principal Investigators, a subset of whom are previous trainees from my lab, who have complementary interests and expertise.

Professor Khalid Naseem

Professor in Cardiovascular Biology, University of Leeds

Keynote: *New models of platelet hyperactivity - the proinflammatory platelet*

Khalid 's research is focused on understanding the molecular mechanisms that regulate platelet activation in both health and disease.

Professor Sue Ozanne

Metabolic Research Laboratories,

University of Cambridge.

MRC Metabolic Disease Unit

Keynote: *Programming by maternal overnutrition: A developing obesity crisis*

The major focus of our research is to understand the mechanistic basis underlying the relationships between sub-optimal early life nutrition and subsequent increased risk of cardiovascular disease, type 2 diabetes, obesity, and premature death. The concept that nutrition and other environmental exposures in early life impact on our long-term health has been termed the Developmental Origins of Health and Disease (DOHaD). Initial studies focussed on the long term detrimental consequences of fetal under nutrition, however it is now widely recognised that other exposures such as maternal stress, maternal over-nutrition and fetal hypoxia have similar “programmed” effects later on in life. Support for this has come from studies in humans and animal models that have allowed causal effects to be demonstrated. Despite extensive evidence for the existence of DOHaD, the molecular mechanisms underlying the process remain poorly understood. To explore the underlying mechanisms we incorporate the study of both rodent models (reflecting both maternal under-nutrition and maternal over-nutrition) and human biopsy material (including muscle, adipose tissue and placenta). We carry out analysis at the whole body, cellular and molecular levels. In some of our most recent studies we are investigating potential intervention strategies using both lifestyle and pharmacological approaches.

Dr Magnus Althage

Team Leader in Translational Science.

Cardiovascular and Metabolic Diseases, AstraZeneca

Keynote: *From Bench to Bedside through translatable in vitro models*

I lead and develop a team of senior scientists, PhD-students, post-docs and masters students. We support the CVMD Innovative Medicine Unit with target validation and biomarker generation through clinically relevant in vitro models. We are actively involved in drug discovery and development from target identification until phase 2 clinical trials. My specific interests lie in developing human systems/models that allow us to improve biological understanding, test novel hypothesis and generate clinically relevant biomarkers. I believe that by establishment of these translatable models we can develop innovative drugs faster to improve quality of life for patients.

In addition, I am convinced that research is done best in collaboration with people and that bring me energy and engagement.

Dr Duncan Richards

Medicine Development Leader,

GlaxoSmithKline

Keynote: *Anti-SAP treatment for systemic amyloidosis; the value of mechanistic models*

In systemic amyloidosis, disease is caused by the extracellular accumulation of amyloid fibrils which progressively disrupt tissue architecture and function. Directly targeted measures are required to specifically remove amyloid deposits in order to preserve and possibly restore organ function. The normal plasma protein, serum amyloid P component (SAP) binds to amyloid fibrils of all types and is always present in amyloid deposits. Acute administration of miridesap, swiftly depletes circulating SAP but leaves some in amyloid deposits as an amyloid-specific antigen target. Repeated administration of the obligate therapeutic partnership of miridesap with appropriate doses of anti-SAP antibody, progressively removed amyloid from the liver and other organs, including the kidney. Up to three antibody doses were given at intervals to patients, mostly with AL or AFib amyloidosis. Treatments were generally well tolerated. Infusion reactions were largely mitigated by hydrocortisone and antihistamine premedication. Pharmacodynamic responses were associated with an early transient inflammatory cytokine response and increased CRP and SAA production, followed by substantial depletion of plasma C3. Pharmacodynamic responses were sometimes associated with self limiting cutaneous rashes. Reduced amyloid load was demonstrated by radiolabelled SAP scintigraphy (liver, spleen, kidneys), extracellular volume measurement by equilibrium MRI (liver, spleen) and liver stiffness determined by transient elastography. Abnormal liver function tests improved following clearance of hepatic amyloid. These preliminary observations demonstrate that progressive amyloid removal can probably be achieved in all types of systemic amyloidosis by repeated courses of miridesap and anti SAP antibody. A phase II study is now planned.

Oral Abstracts

Developmental Programming of Cardiometabolic Disease

IGF2 DELETION FROM THE PLACENTAL ENDOCRINE LAYER ALTERS MATERNAL SENSITIVITY TO GLUCOSE AND INSULIN, AND AFFECTS FETAL AND EARLY POSTNATAL GROWTH IN MICE

*HEJ Yong[1], J Lopez-Tello[1], I Sandovici[2,3], M Constancia[2,3], AN Sferruzzi-Perri[1]

[1]Centre for Trophoblast Research, Department of Physiology, Development and Neuroscience, University of Cambridge. [2]Metabolic Research Laboratories, and MRC Metabolic Diseases Unit, Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge. [3]Department of Obstetrics and Gynaecology, University of Cambridge.

The placenta, the site of maternal-fetal exchange, is a key endocrine organ and regulator of fetal growth. Past studies demonstrated that placental-derived hormones have metabolic effects and may thereby impact the maternal nutrient availability for fetal growth. However, the precise relationship between placental endocrine function, maternal metabolism, and fetal and postnatal growth is unclear. Insulin-like growth factor 2 (*Igf2*), is a paternally expressed imprinted gene, which drives placental endocrine cell formation. Therefore, the study aim was to determine the effect of selective *Igf2* deletion from the endocrine layer of the placenta on maternal metabolism, and fetal and postnatal growth in mice.

TpbpaCre females were crossed with *Igf2*-floxed males to produce whole litters with specific *Igf2* deletion in the placental endocrine layer (leaving placental transport zone, fetus and mother un-manipulated). Dams from the reverse cross were used as controls. On day(D) 16 of pregnancy (term~D20), dams were subjected to glucose or insulin tolerance tests before being sacrificed for tissue collection. A separate cohort of mice were allowed to deliver, litters reduced to 6 pups on postnatal D3 and followed up to weaning.

Dams with placental endocrine *Igf2* deletion failed to acquire pregnancy-induced glucose intolerance and insulin resistance. They also had smaller litters and fetuses, compared with controls. Pup weights were reduced until postnatal D3, but were normalised by weaning. These findings suggest the placental endocrine *Igf2* plays an important role in adapting maternal metabolism and regulating intrauterine and postnatal growth. The long-term metabolic phenotype of the offspring is currently being investigated.

Supported by funding from the Agency for Science, Technology and Research, and the Royal Society.

WHAT'S THAT SMELL? FIRST EVIDENCE OF CARDIO-PROTECTIVE ACTIONS OF HYDROGEN SULPHIDE IN THE DEVELOPING HEART

*RM Hess[1], Y Niu[1,2], TA Garrud[1], KJ Botting[1,2], SG Ford[1], DA Giussani[1,2]

[1]Department of Physiology Development & Neuroscience. [2]Cambridge Cardiovascular Strategic Research Initiative, University of Cambridge, United Kingdom.

Introduction: In the adult individual, pungent hydrogen sulphide (H_2S) is a recognised gasotransmitter conferring cardiac protection. Whether H_2S protects the fetal heart is completely unknown. Here, we show using a chick embryo model that H_2S confers ischaemic preconditioning via activation of K_{ATP} channel opening in the developing heart.

Methods: Hearts isolated from 19-day old chick embryos (term is 21 days) were mounted on a Langendorff preparation. Following basal function recording, hearts were randomly treated with water vehicle (Control), H_2S donor (NaHS), NaHS with the K_{ATP} inhibitor Glibenclamide (NaHS+Glib) or vehicle with Glib (Control+Glib); all drugs at 1mM. After 10 min of treatment, global ischaemia was induced for 30 min. Following 2h of reperfusion, hearts were processed for infarct size analysis. Comparisons for statistical significance used Two-way RM ANOVA.

Results: In control embryos, ischaemia led to significant depression in cardiac function and an increase in infarct size (Fig. 1 A-C). Administration of NaHS prior to ischaemia restored cardiac function towards basal levels and protected against infarction; beneficial effects blocked by combined pre-treatment with Glib. Administration of Glib prior to ischaemia had no effect on cardiac function or infarction. Administration of NaHS increased CFR during baseline and post I/R (Fig. 1D). However, this effect was not prevented by combined pre-treatment with Glib.

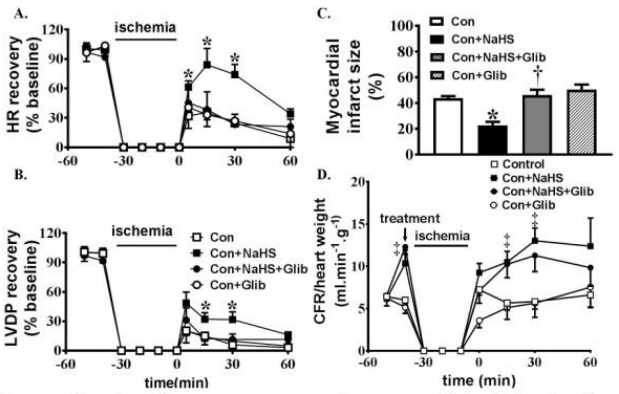

Figure 1. Cardiac recovery and myocardial infarct size measurement following I/R. Values are mean±S.E.M. for heart rate (HR, A), left ventricular developed pressure (LVDP, B), myocardial infarct size (C) and relative coronary flow rate (CFR, D). N=7-10 for each group. Significant differences ($P<0.05$) are: for A and B, *Con+NaHS *vs.* all, AUC; for C, *Con *vs.* Con+NaHS; †Con+NaHS *vs.* Con+NaHS+Glib; for D, ‡Con/Con+Glib *vs.* Con+NaHS/ Con+NaHS+Glib, AUC. Two way ANOVA + Tukey test.

Conclusion: Treatment with a H_2S donor confers protection to the developing heart via opening of myocardial K_{ATP} channels and not via increasing CFR. H_2S may prove a useful therapeutic agent to precondition the fetal heart against IR injury.

Supported by the British Heart Foundation and The Lister Institute

SEX-SPECIFIC PROGRAMMING OF CARDIAC BIOENERGETICS BY CHRONIC HYPOXIC PREGNANCY AND MITOCHONDRIA-TARGETED ANTIOXIDANT THERAPY

*AM Spiroski[1,2,3], MP Murphy[2,3,4], AJ Murray[1,2,3], DA Giussani[1, 2]

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Background: Fetal cardiac mitochondria, exquisitely sensitive to oxygen, adapt to prenatal hypoxia predominantly via Complex I (CI). MitoQ is protective against oxidative stress in adults, but its prenatal applicability is unknown. Thus, we assessed sex-specific cardiac bioenergetics in adult offspring of hypoxic pregnancy, and prenatal MitoQ.

Methods: Pregnant Wistars were exposed to normoxia (N; 21% O_2) or (hypoxia (H; 13% O_2) from 6-20 days gestation ± MitoQ (200μM drinking water; NM, HM). Cardiac mitochondrial respiration was assessed in females (N, n=12-18; H, n=9-12; HM, n=5-8; NM, n=8-13) and males (N, n=5-8; H, n=6-7; HM, n=5-7; NM, n=6-8). Oxygen consumption (O2C: nmol $O_2 \cdot min^{-1} \cdot mg$ wet $weight^{-1}$) was measured by the addition of CI (pyruvate; PY) and β-oxidation (palmitoylcarnitine; PC) substrates, with malate (PY-M, PC-M), in the absence (State 2; S2) and presence (State 3; S3) of ADP; respiratory control ratios (RCRs) were calculated. S3 CIV was measured with *N, N, N', N'*-tetramethyl-p-phenylenediamine and ascorbate (TMPD-A).

Results: Males showed increased pyruvate-mediated CI O2C and decreased RCR; MitoQ improved the latter (Fig. 1A). Hypoxia increased CI β-oxidation RCR in males, which was restored by MitoQ (Fig. 1B). MitoQ reduced β-oxidative coupling and S3 CIV O2C in both sexes (Fig. 1B, C).

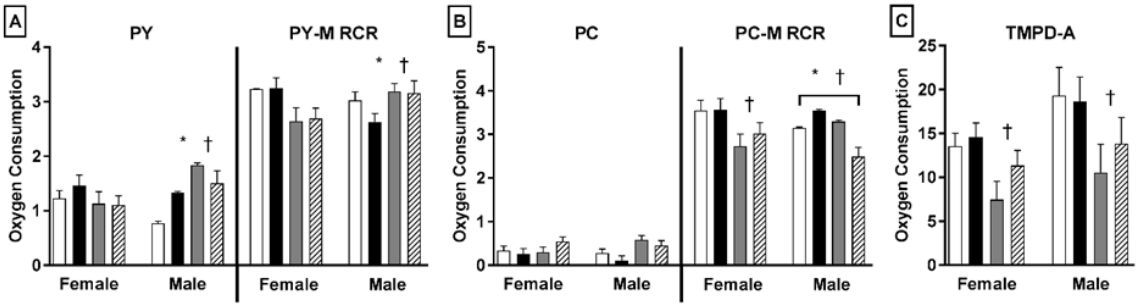

Figure 1. CI, A and B, and (C) S3 TMPD-A. Data are means ± SEM for offspring (N, white; H, black; HM, grey; NM, hashed). Statistical differences, $p<0.05$: main effect of *hypoxia; †MitoQ; hypoxia x MitoQ interaction indicated by brackets (Two-Way ANOVA with Tukey's *post-hoc*).

Conclusions: Prenatal hypoxia programmes sex-specific cardiac bioenergetics in adulthood. Whilst female hypoxic offspring appear protected, males have poorer CI and β-oxidative coupling. MitoQ improves pyruvate-mediated CI coupling and β-oxidative uncoupling in hypoxic males, and reduces CIV O2C in all adults. MitoQ shifts bioenergetic flux through anaerobic pathways, reducing cardiac oxygen demand in adulthood.

Supported by the British Heart Foundation

Inflammation and Platelets in Cardiometabolic Disease

MARGINAL ZONE B CELLS LIMIT TFH DIFFERENTIATION IN ATHEROSCLEROSIS IN RESPONSE TO A HIGH CHOLESTEROL DIET

*M Nus, A Sage, Y Lu, S Newland, Z Mallat

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Atherosclerosis is the leading cause of death and morbidity worldwide. It is a complex inflammatory disease in which immune and vascular cells, and inflammatory and lipid mediators participate. I have recently made an important discovery that a specific B cell subset, called marginal zone B (MZB) cells, protects against high fat and high cholesterol diet (HF/HCD)-induced atherosclerosis in mice and that this protection occurs through modulation of follicular helper T (Tfh) cells (*1*), a recently discovered subset that plays a detrimental role in atherosclerosis (*2*). I have also identified that the absence of MZB cells results in impaired Tfh cell differentiation, which is likely to significantly contribute to the anti-atherogenic properties of MZB cells but we do not know how this is modulated. We have performed RNA-seq analysis and identified a set of genes that were significantly differently expressed on splenic Tfh cells sorted from low-density lipoprotein receptor deficient (*Ldlr*$^{-/-}$) mice (a strain susceptible to hypercholesterolemia and atherosclerosis) with MZB cells (normal Tfh) or without MZB cells (‘aberrant’ Tfh) fed a HF/HCD for 8 weeks (*1*). Ingenuity analysis and gene set enrichment analysis of our RNA-seq data identified several metabolic pathways that are differently expressed between ‘aberrant’ and normal Tfh cells, suggesting the potential importance of metabolism modulating Tfh cell differentiation.

1. **M. Nus** *et al.*, Marginal zone B cells control the response of follicular helper T cells to a high-cholesterol diet. ***Nat. Med.*** 23, 601–610 (2017).

2. M. Clement *et al.*, Control of the T follicular helper-germinal center B-cell axis by CD8(+) regulatory T cells limits atherosclerosis and tertiary lymphoid organ development. *Circulation*. 131, 560–570 (2015).

Supported by the British Heart Foundation

IS DE NOVO LIPOGENESIS A DRIVER OF FIBROSIS IN NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)?

*V Azzu, M Vacca, A Archarjee, S Virtue, M Dale, S Carobbio, G Bidault, I Huang-Doran, A Koulman, J Griffin, A Vidal-Puig and M Allison

Department of Medicine, University of Cambridge.

NAFLD, the largest cause of chronic liver disease worldwide, is caused by an abnormal accumulation of lipids in the liver potentially inducing hepatic lipotoxicity, inflammation and fibrosis. We recruited 200 patients with biopsy-proven steatohepatitis (NASH) from the Cambridge NASH clinic. Clinical and biochemical data were integrated with hepatic RNA sequencing (n:57) and serum lipidomics (DI-MS, n: 82) data. Transcriptomic analysis as a function of disease stage (activity and fibrosis) suggested the activation of pro-inflammatory and pro-fibrotic pathways. “Upstream regulators” in IPA analysis pointed to Insulin-Induced Gene 1 (INSIG1) as a key regulator of these processes, also correlating with fibrosis severity. INSIG1 is an inhibitor of de novo lipogenesis (DNL) and cholesterol biosynthesis. INSIG1 expression negatively correlated with expression of DNL genes (e.g. FASN and SCD1), which positively correlated with a triglyceride signature enriched in products of DNL (TG46:2/TG48:2/TG48:1/TG50:1) and associated with NAFLD.

We are now dissecting the role of INSIG1 in NAFLD/NASH transition, using the INSIG1 KO mice. Preliminary data show that metabolic parameters (lipid and glucose profile) and histology do not differ in INSIG1 KO mice (vs. WT) on a chow diet. Nevertheless, upregulation of genes involved in DNL (FASN, SCD1, ELOVL6), cholesterol synthesis (HMGCS1, HMGCR), inflammation (CCL5, TNFa, F4/80) and fibrosis (Col4) can be observed in KO by qPCR. Also, bone-marrow-derived macrophages are more pro-inflammatory implicating INSIG1 as a potential driver of systemic inflammation and NASH. Future work will address the relevance of INSIG1 in dietary models of NASH and in chemical models of fibrosis (CCl4).

We would like to thank Agnes Lukasic for genotyping, core, histology, imaging, sequencing and animal facilities. Funding bodies: MRC, Wellcome Trust, University of Cambridge, BHF, Evelyn Trust, CUH NFT

INHIBITING TMEM16F, A PLATELET SCRAMBLASE

*SL Burgess, T Rahman, MT Harper

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Rationale: The anti-thrombotic drugs currently in use increase the risk of adverse bleeding events as they affect a wide range of platelet signalling pathways. Platelet phosphatidylserine (PS) exposure generates a pro-coagulant surface which contributes to thrombosis but which occurs only in a subset of activated platelets. PS exposure is not targeted by current anti-thrombotic drugs. PS exposure in platelets and erythrocytes requires activation of a scramblase protein, TMEM16F. Here we seek to identify lead compounds for design of a TMEM16F inhibitor, in order to test whether inhibition of TMEM16F is a useful anti-thrombotic strategy.

Methods: Polyphenolic compounds were assayed for effects on erythrocyte PS exposure. Flippase activity was inhibited by 10 mM N-Ethylmaleimide (NEM). Erythrocytes were then incubated with compounds for 10 minutes before being stimulated for 30 minutes at 37°C using 0.4 µM A23187 and 100 µM extracellular Ca^{2+}. PS exposure was measured using Annexin V binding by flow cytometry. A homology model of hTMEM16F was generated and refined using multiple template based modelling algorithms.

Results and conclusions: 100 µM Tannic Acid and 100 µM epigallocatechin gallate (EGCG) inhibit PS exposure in erythrocytes. An empirical screen of catechin compounds identified that an associated gallate group is necessary for inhibition of PS exposure, whilst gallocatechins were identified low level activators of PS exposure. Initial models suggest that bioactive compounds bind TMEM16F at sites critical for PS exposure. Future work will examine these ligand-protein interactions in greater detail to predict additional compounds that bind the same site as these polyphenolic compounds.

Funded by the British Heart Foundation 4-Year PhD Scheme

Mechanisms of Obesity and its Cardiometabolic Effects

EFFECT OF MATERNAL EXERCISE DURING OBESE PREGNANCY ON THE CARDIOVASCULAR HEALTH OF MALE MOUSE OFFSPRING

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Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge.

Background. In the UK over half of women of childbearing age are overweight or obese. This is concerning as maternal obesity is associated with short and long-term risks to both mother and child. Studies in humans have suggested that individuals born to obese mothers are at increased risk of cardio-metabolic disease and premature death from cardiovascular disease. Strong evidence from animal models shows this is partly mediated by non-genetic *programmed* mechanisms. Interventions to prevent the propagation of poor health are therefore urgently needed. This study aimed to investigate the effect of exercise during obese pregnancy on the offspring's cardiovascular health.

Methods. A maternal diet-induced obesity mouse model was used where female dams are fed an obesogenic diet (high fat and sugar) prior to and during pregnancy. Obesogenic diet-fed mice were treadmill exercised (5 days/week) during mating and pregnancy (up to E17). Offspring were weaned onto standardized chow with males studied at 8 weeks old. Blood pressure and *in vivo* cardiac function were measured by tail-cuff photoplethysmography and echocardiography.

Results. Offspring from obese dams (ObeseOff) had pathological cardiac hypertrophy [increased heart weight ($p<0.001$) and cardiomyocyte area ($p<0.05$)], cardiac dysfunction and increased systolic blood pressure ($p<0.01$). Maternal exercise prevented the cardiac dysfunction and hypertrophy but not the increased blood pressure.

Conclusions. The programming of cardiac dysfunction and hypertension could occur independently. Maternal exercise during an obese pregnancy has therapeutic effects on some aspects of cardiovascular health of the offspring but not others. Further work is needed to understand the underlying mechanisms.

Supported by the British Heart Foundation

SREBP1 MEDIATED DE NOVO LIPOGENESIS SEQUESTERS NADPH TO INACTIVATE MACROPHAGES ANTIOXIDANT DEFENCES AND PROMOTE THEIR ALTERNATIVE ACTIVATION.

*G Bidault, S Virtue, K Petkevicius, S Carobbio, A Kaser and A Vidal-Puig

Metabolic Research Laboratories, Institute of Metabolic Science.

Rationale: Enhanced macrophage alternative activation (M2) protects against obesity-associated cardiometabolic complications. Importantly, macrophage activation rewires its metabolism to power the immune response. Interleukin 4 (IL-4) triggering of alternative activation of macrophages requires enhancement of lipid and glucose utilization. We hypothesised that the *de novo* lipogenesis (DNL) pathway, under the transcriptional control of sterol regulatory element binding protein 1 (SREBP1), link glucose and lipid utilization in M2 macrophages

Methods: We use primary murine macrophages and a mouse model in which SREBP1 cannot be activated specifically in the macrophages population to determine a) whether SREBP1 is activated in M2 macrophages and b) the importance of SREBP1 and the DNL in M2 macrophages.

Results: SREBP1 is rapidly activated by IL-4 in an AKT-dependent manner, resulting in upregulation of the DNL program, thus intertwining glucose and lipid metabolism. SREBP1 activation is required for macrophages M2 polarisation *in vivo* and *in vitro*. Moreover, activation of the DNL program consumes NADPH and decreases NADPH dependent antioxidant defences. Thus, by directly reducing antioxidant defences in macrophages, activation of SREBP1 enables accumulation of mitochondria-derived reactive oxygen species, which is required for the maintenance of the active phosphorylated form of STAT6, an IL-4 induced transcription factor, which is essential M2 polarisation.

Conclusion: We identified and explored a metabolic pathway fine-tuning macrophages alternative activation, linking glucose and lipid metabolism with redox status and signal transduction.

Supported by the British Heart Foundation

INVESTIGATING THE AETIOLOGIC LINKS BETWEEN THE GUT MICROBIOTA, METABOLIC PROFILES AND METABOLIC DISEASE

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The gut microbiota has been associated with a wide range of cardiometabolic diseases and risk factors and is thought to influence host health systemically by producing nutrients, or 'metabolites'. However, few studies have assessed a causal role for the gut microbiota in humans.

This study had two objectives: 1.) to determine whether microbial metabolites are associated with BMI, weight change prior to baseline or prospective weight change; and 2.) to determine whether the type 2 diabetes (T2D)-associated metabolite pool is enriched with microbial metabolites. Previously-profiled serum samples from 7,503 individuals, 1,503 of whom form a T2D case-control cohort, were taken from the EPIC-Norfolk cohort for this study.

Microbial metabolites were identified through literature review and with the help of Metabolon Inc. Linear regression analyses were performed between i.) prior weight change, ii.) BMI at baseline, or iii.) prospective weight change and metabolite concentrations. A Prentice-weighted Cox proportional hazards regression was used to assess metabolites in the T2D-associated metabolite pool.

Results showed that common and unique microbial metabolic pathways were associated with prior weight change and BMI, though no microbial metabolites were associated with prospective weight change. The study lacked power to detect associations between microbial metabolites and T2D.

This study provides preliminary insights into the role of gut microbial metabolism in human metabolic profiles and disease. Future steps include performing association analyses between metabolite concentrations and a BMI genetic score and repeating all analyses for waist-hip ratio, which is a measure of central adiposity and another risk factor for T2D.

The authors would like to thank Metabolon Inc. for their assistance in classifying microbial metabolites.

Poster Abstracts

DEVELOPMENT OF AN ANTAGONISTIC GLP1R ANTIBODY TO BLOCK GLP-1 SIGNALLING IN VIVO

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Glucagon like peptide-1 (GLP-1) and GLP-1 mimetics enhance glucose-dependent insulin secretion by binding to GLP-1 receptors (GLP1R) on pancreatic beta cells. Despite the therapeutic success of GLP-1 mimetics for the treatment of type 2 diabetes, several clinical effects of GLP-1 remain unexplained at a mechanistic level, particularly in extra-pancreatic tissues such as the cardiovascular system. The objective of this study was to generate and characterise a monoclonal antagonistic antibody for the GLP1R that can be used to block GLP1R signalling in vivo.

Naïve phage display led to the selection of Glp1R0017, an antagonistic antibody against mouse, human, rat, cyno and dog GLP1R. This antagonistic activity was specific to GLP1R, with no activity in functionally related GPCRs. Functional activity was confirmed in INS-1 832/3 cells using live cell cAMP imaging and insulin secretion experiments. Immunostaining of mouse pancreas tissue with Glp1R0017 showed specific staining in the islets of Langerhans, not observed in GLP1R KO tissue. In vivo, Glp1R0017 reversed the glucose-lowering effect of liraglutide during ipGTT in mice. Glp1R0017 also blocked the effects of endogenous GLP-1 on glucose tolerance, shown by OGTT in mice.

This antibody holds the potential to further understand the cardiovascular actions of GLP-1. As the GLP1R is becoming more widely targeted using both specific agonists and dual agonists, there is particular therapeutic interest to understand cardiovascular effects of GLP-1. Glp1R0017 combined with the use of cardiac telemetry, can provide a novel strategy to investigate the effect of GLP-1 in the cardiovascular system.

The authors wish to thank the BSU staff at MedImmune for help with running the glucose tolerance tests, and the funding bodies MedImmune and Cambridge BRC for the PhD studentship. Also, thanks to Wellcome Trust and MRC for centre funding.

THE ROLE OF THE *IGF2-H19* IMPRINTED LOCUS IN REGULATING PLACENTAL ENDOCRINE FUNCTION IN THE MOUSE WITH CONSEQUENCES ON MATERNAL METABOLISM AND FETAL GROWTH

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During pregnancy, the mother must adapt metabolically to support fetal growth. Failure in maternal adaptation can result in gestational diabetes and fetal growth abnormalities. The placenta secretes hormones with metabolic effects, although the precise role of placental endocrine function in maternal metabolic health and fetal development is largely unknown. Insulin-like growth factor-2 (*Igf2*) is a growth gene that promotes placental endocrine function and conceptus development. *Igf2* and the neighbouring *H19* gene are subject to parental imprinting (*Igf2* being expressed only from paternal and *H19* from maternal allele, respectively) and both are under the control of the differentially methylated region (*DMR*) located upstream *H19*. Therefore, this study aimed to determine the effect of over-expressing *Igf2* in the placental endocrine junctional zone (Jz-*Igf2*OE) on maternal metabolism and feto-placental growth in mice.

On day (D) 16 of pregnancy (term=D20), dams with Jz-*Igf2*OE (achieved by activation of the normally silent maternal *Igf2* copy in the Jz, *H19DMR/TpbpaCre*) were hyperglycemic, hyperinsulinemic and hyperleptinemic in fed conditions. Abundance of the insulin signalling pathway and glucose transporter-4 was diminished or unchanged in the adipose tissue and skeletal muscle of these Jz-*Igf2*OE dams. There was however, no significant change in the glucose or insulin tolerance following challenge in fasted Jz-*Igf2*OE dams. Jz size and *Igf2* expression were increased and maternal plasma IGF2 concentration and fetal weight unaltered in response to Jz-*Igf2*OE. Overall, these data suggest perturbed maternal glucose-insulin handling in response to Jz-*Igf2*OE.

This work was supported by funding from the Agency for Science, Technology and Research and the Royal Society.

MITOHORMESIS: CARDIOPROTECTION BY THE SUPEROXIDE GENERATOR MITOPARAQUAT IN A MOUSE MODEL OF ACUTE MYOCARDIAL INFARCTION

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Rationale Myocardial infarction, occurring when the blood supply to the heart is disrupted and then restored, is a leading cause of death and disease worldwide. Mitochondrial reactive oxygen species (ROS) play a central role in the formation of the infarct, yet the use of antioxidant supplements in large scale clinical trials has shown no beneficial effects and some studies have even suggested that the addition of exogenous ROS in experimental settings may decrease infarct size. This suggests that mitochondria may exhibit a biphasic response to ROS, termed mitohormesis, characterised by beneficial effects at low dosages and detrimental effects at high dosages.

Methods To investigate this phenomenon, a tool is required to precisely titrate mitochondrial ROS. MitoParaquat is a novel mitochondria-targeted molecule that redox cycles at complex I to produce superoxide, closely mimicking the production of ROS *in vivo*. Here it is validated both *in vitro* and *in vivo* and then used to investigate the role of ROS in protection against acute myocardial ischaemia reperfusion injury.

Conclusions First and foremost, the generation of low doses of exogenous ROS by MitoParaquat is shown to be protective against acute myocardial IRI *in vivo*. MitoParaquat is shown to exhibit a dose response curve indicative of mitohormesis, with protection conferred only in an intermediate dose range with high doses found to be lethal and infarcts from low dose not significantly different from control.

Supported by the MRC, and the Raymond and Beverly Sackler Fund

OPTIMISING THE CULTURE CONDITIONS OF MOUSE PLACENTAL ENDOCRINE CELLS FOR DOWNSTREAM SECRETOME ANALYSIS

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During pregnancy, many physiological changes occur in the mother that enable the support of fetal growth. These include changes in the maternal cardiovascular, immune and metabolic systems, and are signalled, in part, by changes in placental hormone production. However, a complete identification of the proteins secreted by the placenta that mediate the changes in maternal physiology is lacking. This study aimed to establish a culturing method for placental endocrine cells from which secretory output could be collected and unbiasedly characterised. Mouse was used as a research model as the endocrine and transport functions are performed by discrete zones that can be physically separated. Whole placenta (WP) and isolated endocrine junctional zones (Jz) were obtained on day 16 (maximal Jz size). WP and Jz trophoblast were then isolated by density-gradient centrifugation, seeded at 104 cell/ml and cultured for up to 120h (n=6). In both WP and Jz cultures, approximately 20% of the cells were lost within 24h of culture, and a further 20% were lost by 48h. Cell proliferation was detected at 72h and 96h, probably reflecting fibroblast contamination and expansion. By 120h, the majority of WP and Jz cells were not viable. Protein concentration of the conditioned media increased by 66% and 44% in Jz and by 225% and 25% in WP at 24h and 48h, respectively (n=3). Density of endocrine versus transport trophoblast cells in cultures are being investigated. Establishment of optimal conditions for culturing placental endocrine cells will be followed by mass spectrometry analysis of the secretome.

This research is supported by the Marie Skłodowska-Curie action (IF) and the Royal Society Dorothy Hodgkin Fellowship awarded to A.N. Sferruzzi-Perri

ROLE OF THE PROLIDASE PEPD IN MACROPHAGES AND ADIPOSE TISSUE FIBROSIS IN OBESITY

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Adipose tissue (AT) of obese metabolically compromised patients is dysfunctional and exhibits Fibro-inflammation. Here we investigate the role of prolidase, PEPD, a key enzyme involved in collagen degradation. We hypothesize that obesity promotes impairment of PEPD-dependent degradation of fibrosis limiting AT expansion/function.

We initially found that PEPD prolidase was particularly expressed in macrophages and it expression and enzymatic activity were downregulated in AT from obese mice in association with fibrosis while it serum levels were increased suggesting a release from damaged cells. Resulting extracellular PEPD acted as pro-inflammatory and pro-fibrotic factors on both macrophages and preadipocytes increasing collagen production and inhibiting adipogenesis through EGFR-dependent pathways. We found that both genetical (KO) and pharmalogical (CBZ-Pro) PEPD inhibition lead to AT fibrosis when fed in chow diet and resistance to HFD-induced obesity suggesting impaired tissue plasticity and expansion. This was particularly associated with defective differentiation/polarization of macrophages, glucose intolerance and insulin resistance.

Taking together, these results suggest a role of PEPD prolidase in macrophages functions and the progression of adipose tissue fibrosis during obesity. Signalling pathways regulating/regulated by PEPD function need to be determine and could represent potential therapeutical targets in order to preserve AT functionality in obesity.

All animal work was carried out in the Disease Model Core, part of the MRC Metabolic Diseases Unit [MRC_MC_UU_12012/5] and Wellcome Trust Strategic Award [100574/Z/12/Z]. This work was funded by the Medical Research Council (MRC), the Metabolic Diseases Unit of the MRC, European Commission http://dx.doi.org/10.13039/501100000780 grant FP7-ETHERPATHS, and by the British Heart Foundation396 (RG/12/13/29853).

IMPACT OF FILAMIN A DEFICIENCY IN PULMONARY ARTERY SMOOTH MUSCLE CELLS

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Pulmonary arterial hypertension (PAH) arises from the extensive remodelling of the pulmonary arteries which results in elevated pulmonary vascular pressure and consequently right heart failure. While mutations in the bone morphogenetic protein (BMP) type II receptor (BMPR-II) have been shown to account for 80% of heritable and 25% of idiopathic PAH, the remaining cases are unaccounted for.

Recently, a genome wide association study involving PAH patients has identified Filamin A as a potential rare causative gene in a subset of PAH patients without BMPR2 mutations. Through structural analyses, these missense mutations cluster within *s*mall *m*other *a*gainst *d*ecapentaplegic (SMAD)-binding domains, implicating the potential involvement of Filamin A mutants in dysregulated TGFβ- and/or BMP-mediated SMAD signalling pathways.

To investigate the role of Filamin A in SMAD signalling, *FLNA* was silenced by transfecting human PASMCs with siRNAs. Knockdown efficiency was evaluated by mRNA and protein expression. TGFβ and BMP signalling pathways were examined by comparing the expressions of known downstream targeted genes, namely *ID1*/*ID2* (BMP-responsive) and *PAI1*/*CTGF* (TGFβ-responsive). While BMP signalling appears unaffected, a reduction in CTGF expression suggested compromised TGFβ signalling. This observation is consistent with impaired signalling through the canonical TGFβ-responsive second messenger, SMAD3.

Previous studies have found PASMCs harbouring BMPRII mutations to show characteristics of dysregulated TGFβ pathway. Preliminary data from proliferation assays suggested FLNA-deficient PASMCs to be resistant to growth inhibition in response to TGFβ, thereby suggesting that the loss of FLNA activity mirrors that of BMPRII. The mechanistic details behind such phenomenon is now further investigated.

I would like to thank my supervisors, Professor Nicholas Morrell and Dr. Paul Upton for their constant scientific guidance and tireless patience throughout the progress of this study. I would also like to extend my gratitude to all the members within the Morrell Laboratory for their friendly advice and encouragement. And finally, thank-you to Wellcome Trust for funding this study.

MECHANISMS OF HYPERTENSION FOLLOWING TREATMENT WITH ERYTHROPOIESIS-STIMULATING AGENTS: THE OPERA-CKD PILOT STUDY

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Rationale: Conventional erythropoiesis-stimulating agents (ESAs) represent standard care treatment for anaemia of chronic kidney disease. ESAs induce hypertension and increase cardiovascular (CV) risk through an unknown mechanism. We hypothesize this to be driven by either endothelial dysfunction and/or vasoconstriction. We describe the design and progress of a mechanistic pilot study (NCT 02987465) to assess the effect of ESAs on candidate vascular regulatory pathways. Here, we report preliminary baseline characteristics.

Methods: This study aims to enrol 12 ESA-naïve patients requiring *de novo* treatment for clinical reasons, and 12 control subjects. Participants undergo forearm blood flow (FBF) plethysmography before and 6-weeks after commencing darbepoetin-alpha. Control subjects undergo study procedures at baseline only. FBF is assessed after intra-arterial acetylcholine, noradrenaline and BQ123 administration to assess endothelial dependent, vasoconstrictor and endothelin-A dependent pathways respectively.

Results: Between April 2017 and October 2017, we enrolled 9 participants (8 male, 89%) and 3 control subjects (2 male, 67%). Mean age was 67±14 years (cases) and 55±14 years (controls). At baseline, mean haemoglobin (Hb) was lower in cases (99.6±11.5 g/L) than controls (145±9 g/L), and creatinine was higher (284±88 umol/L versus 81±6 µmol/L respectively). Blood pressure (MAP 113±16 mmHg versus 87±12 mmHg) were higher in cases than controls. Recruitment is ongoing.

Conclusions: This pilot study will elucidate the most likely pathway through which the hypertensive response to ESAs is mediated, and will allow the design of intermediate endpoint trials of conventional versus novel treatments for anaemia of CKD.

Funded by GlaxoSmithKline plc

APELIN AND SEROTONIN PARACRINE FUNCTION IN THE GUT: AN USSING CHAMBER BASED STUDY

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APELIN SECRETION & FUNCTION IN THE GUT

Apelin peptides target the APJ GPCR to mediate effects in the cardiovascular system. Recently, glucose-dependent secretion of apelin into the lumen of mouse gut has been observed, where it influences glucose uptake through up-regulation of GLUT2, and down-regulation of SGLT-1 in epithelial cells.

Apelin and APJ mRNA was quantified in gut tissues using qPCR. Apelin mRNA was almost undetectable in all gut tissues sampled, whilst APJ mRNA was low. Ussing chamber secretion samples were analysed using mass spectrometry, which failed to detect apelin in both luminal and basolateral compartments. Ussing chamber short-circuit current studies showed that exogenous apelin did not down-regulate SGLT-1 in mouse jejunum/ileum. Overall, the experiments were unable to confirm the presence of apelin in the gastro-intestinal tract, or its role in SGLT-1 regulation.

GPER REGULATED SECRETION IN THE COLON

Serotonin (5-HT) has been shown to be released in the colon where it stimulates secretion of fluid and mucus. Activation of GPER was hypothesised to stimulate secretion of 5-HT, to stimulate opening of the CFTR Cl- channel on colonic enterocytes.

Ussing chamber short-circuit current studies showed a delayed increase in Cl- current after stimulation with a GPER agonist, with a tendency for block by a GPER antagonist. The agonist response was not blocked by a 5-HT4 receptor selective antagonist, or a 5-HT3 receptor antagonist, indicating that the GPER agonist does not stimulate secretion of 5-HT, or that 5-HT released acts on a different receptor subtype.

Special thanks to F Reimann and F Gribble for allowing this work to be conducted in their laboratories. Thanks also to the Wellcome Trust who provided funding for this research.

DELEGATE LIST

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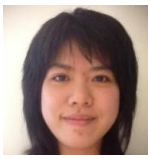
	Caroline Archer AstraZeneca caroline.archer@astrazeneca.com	Develop assays and *in vitro* cardiovascular models for safety assessment at AstraZeneca.
	Victoria Auyeung MRC Epidemiology Unit vpwa2@cam.ac.uk	I am a PhD student researching the clinical characterisation of genetic variation in the general population.
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	Guillaume Bidault Institute of Metabolic Science-Metabolic Research Laboratories gb483@medschl.cam.ac.uk	
	Emma Biggs Institute of Metabolic Science-Metabolic Research Laboratories ekb39@medschl.cam.ac.uk	A GLP1R antagonistic antibody has been developed which could be used to further understand the actions of GLP-1 in the cardiovascular system.

	Heather Blackmore Institute of Metabolic Science-Metabolic Research Laboratories hlb46@cam.ac.uk	Study the impact of maternal diet-induced obesity on the development of cardiovascular disease in the offspring
	Sarah Burgess Department of Pharmacology slb95@cam.ac.uk	Pro-coagulant platelet signalling and anti-thrombotic drug design
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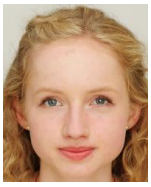
	Andrew Hall AstraZeneca andrew.hall@astrazeneca.com	Investigating cardiac toxicology with regards to metabolism, contractility and conductivity
	Rita Hess Department of Physiology, Development and Neuroscience. rh658@cam.ac.uk	First evidence of the cardio-protective actions of hydrogen sulphide in the developing heart
	Christine Hinz Department of Biochemistry ch768@cam.ac.uk	Lipidomic analysis of biological samples including platelets, plasma, leukocytes, and different tissues using ion mobility mass spectrometry
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	Elizabeth Le Department of Medicine epvl2@cam.ac.uk	
	Jeniffer Leggat Department of Medicine jl687@cam.ac.uk	The effects of hydrogen sulphide treatment on cardiac ischaemia-reperfusion injury in the chick embryo
	Chen Li MRC Epidemiology Unit csli5523@gmail.com	Discovering Cardiometabolic consequences to ageing using Genetics and metabolomics

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	Vanessa Pellegrinelli Institute of Metabolic Science – Metabolic Research Laboratories vp332@medschl.cam.ac.uk	Molecular mechanisms by which dysfunctional white fat leads to lipotoxicity in peripheral organs and how these contribute to the pathogenesis of the metabolic complications of obesity.
	Maria Pires Biosciences and Forensics, Anglia Ruskin University maria.lopes-pires@anglia.ac.uk	Zinc modulates reactive oxygen species generation in platelets
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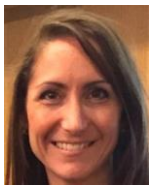
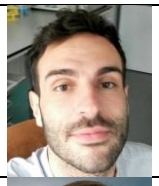
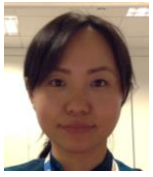
	Josca Schoonejans Institute of Metabolic Science – Metabolic Research Laboratories jms297@medschl.cam.ac.uk	Effectiveness and safety of metformin intervention on programming of cardiometabolic health in offspring of obese pregnancy
	Amanda Sferruzzi-Perri Department of Physiology, Development and Neuroscience ans48@cam.ac.uk	Placental function and its importance for pregnancy and long-term cardio-metabolic health
	Joy Shih Department of Medicine kljs2@cam.ac.uk	Impact of Filamin A deficiency in pulmonary artery smooth muscle cells
	Ana-Mishel Spiroski Division of Experimental Medicine and Immunotherapeutics, Department of Medicine ams261@cam.ac.uk	Mitochondrial re-programming of fetal deprivation, and prevention of adult cardiometabolic disease
	Lucy Spokes External Affairs & Communications lucinda.spokes@admin.cam.ac.uk	
	Luca Stefanucci Department of Haematology ls760@meschl.cam.ac.uk	Chromatin interaction and Super-Enhancers, their involvement in gene expression
	Petra Sulentic Department of Medicine ps743@medschl.cam.ac.uk	I am investigating the haemodynamic and metabolic role of endogenous peptides apelin and relaxin in healthy people and patients with type 2 diabetes mellitus
	Jane Sugars Institute of Metabolic Science – Metabolic Research Laboratories jms80@medschl.cam.ac.uk	
	Zoe Sun Division of Experimental Medicine and Immunotherapeutics, Department of Medicine zs318@medschl.cam.ac.uk	Mechanisms of Hypertension associated with treatment with Erythropoiesis-Stimulating Agents
	Paul Sweeten BHF sweetenp@bhf.org.uk	

	Annabel Taylor Division of Cardiovascular Medicine, Department of Medicine alt55@cam.ac.uk	Heterogeneity in vascular smooth muscle cell phenotypic switching and how this influences their contributions to cardiovascular disease
	Rita Tome Department of Haematology arr50@cam.ac.uk	Uncovering the functions of SMIM1 in blood and other organs
	Toni Vidal-Puig Institute of Metabolic Science – Metabolic Research Laboratories ajv22@medschl.cam.ac.uk	
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	David Whitaker BHF whitakerd@bhf.org.uk	
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