UNIVERSITY OF CAMBRIDGE

Cardiovascular Early Careers Event

2nd annual meeting

Tuesday 13th September 2016

McGrath Centre, St Catharine's College, CB2 1RL

This event is sponsored by the BHF Cambridge Centre for Cardiovascular Research Excellence and the University of Cambridge Cardiovascular Strategic Research Initiative

British Heart Foundation

BHF Cambridge Centre for Cardiovascular Research Excellence

Cardiovascular Strategic Research Initiative

Welcome from the Organising Committee

This is the second time we are organizing this event. Following feedback from last year's launch event, the format has been changed slightly.

Similarly to last year, we will host a TED-style research career keynote talk and will welcome Prof Nicole Soranzo from the Wellcome Trust Sanger Institute. We have also selected talks and posters from various Departments to showcase the breadth of research done in Cambridge.

In an attempt to add a training aspect to the day, the University's Research Communications team (Drs Craig Brierley & Barney Brown) will run two sessions on promoting research – through blogging and Twitter.

Our day will close with a session on how to apply successfully for external Fellowship. Two recently appointed Fellows (Drs Diane Proudfoot & Loes Rutten-Jacobs) will give a short overview of the application process, and the floor will then open for a Q&A session with representatives from the University and funders available to answer questions.

We hope that you will find the day engaging and inspiring!

Aarti, Ana-Mishel, Isabel, Jason, Kat, and Katja

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Programme

08.30 – 09.00 Registration & Tea

Session 1 Biomedical Science (Animal)

09.00 – 09.15 Prof Martin Bennett (Medicine) – *Opening words*

09.15 – 09.30 Dr Kim Botting (Physiology, Development & Neuroscience)
The mitochondrial-targeted antioxidant MitoQ prevents the programming of cardiovascular dysfunction by developmental hypoxia in sheep

09.30 – 09.45 Ms Elena Loche (Clinical Biochemistry)
Maternal over-nutrition programs ventricular remodelling and cardiac dysfunction independently of post-natal diet

09.45 – 10.00 Dr Ana-Mishel Spiroski (Physiology, Development & Neuroscience)
Developmental programming of pulmonary hypertension by chronic prenatal hypoxia

10.00 – 10.30 Professor Nicole Soranzo (Sanger institute) – *Career keynote*

10.30 – 11.00 Tea & Posters

Session 2 Bioengineering

11.00 – 11.15 Dr Marta Serrani (Chemical Engineering & Biotechnology)
Durability prediction for the design of a new polymeric heart valve prosthesis

11.15 – 11.30 Dr Vera Graup (Materials Science & Metallurgy)
Designing scaffold biomaterials for heart tissue repair

11.30 – 11.45 Dr Felipe Serrano (Medicine)
Correction of Marfan mutation C1242Y in human iPS cells using CRISPR/Cas9 technology re-establish normal phenotype in human neural crest-derived smooth muscle cells

11.45 – 12.30 Dr Craig Brierley (Research Communications) – *Promoting research via blogging*

12.30 – 13.30 Lunch

Session 3 Biomedical Science (Bench)

13.30 – 14.15 Dr Barney Brown (Research Communications) – *Promoting research via social media*

14.15 – 14.30 Mr Adam Fellows (Medicine)
FOXO3A induces VSMC apoptosis through MMP-13: implications for atherosclerotic plaque rupture

14.30 – 14.45 Ms Amanda Dalby (Haematology)
Generating an inducible human iPSC line to produce mature megakaryocytes in vitro

14.45 – 15.00 Mr Fedir Kiskin (Medicine)
Development of iPSC models of pulmonary arterial hypertension

15.00 – 15.30 Tea & Posters

Session 4 Clinical

15.30 – 15.45 Dr Eleni Sofianopoulou (Public Health & Primary Care)
Modelling seasonal and spatio-temporal variation: the example of respiratory prescribing

15.45 – 16.00 Mr Shuo Wang (Radiology)
Structural and flow-diverting effects of multiple overlapping uncovered stents: a novel management strategy for thoracoabdominal aortic aneurysm

16.00 – 16.15 Dr Nicholas Evans (Clinical Neurosciences)
Non-invasive identification of culprit carotid atheroma using sodium fluoride-positron emission tomography

16.15 – 17.00 Dr Diane Proudfoot (Babraham Institute) & Dr Loes Rutten-Jacobs (Clinical Neurosciences) – *Fellowship application talks followed by Funding Panel Q&A*

17.00 – 18.00 Prizes & Closing words, Drinks Reception

Keynote speaker

Prof Nicole Soranzo, Wellcome Trust Sanger Institute

Nicole was trained in quantitative population and statistical genetics at the University of Milano, University of Dundee and University College London, where she applied genetic analysis to evolutionary studies of natural populations and human traits.

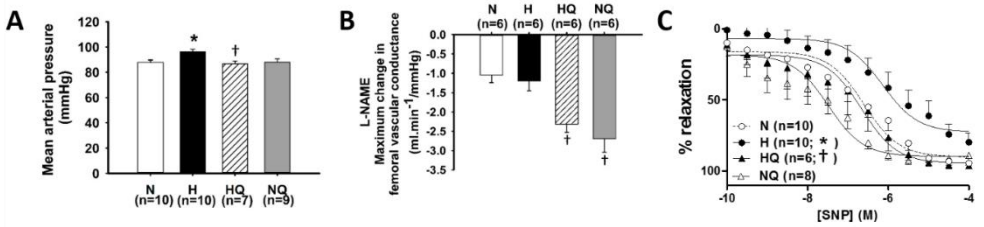
She spent two years in the pharmaceutical industry in the US, applying human genetics to improve drug discovery and pharmacogenomics.

She returned to the UK at the Sanger Institute, where she started her group in 2009. In 2013 she became adjunct faculty at the University of Cambridge, School of Clinical Medicine, and in 2015 was awarded a personal Chair in Human Genetics.

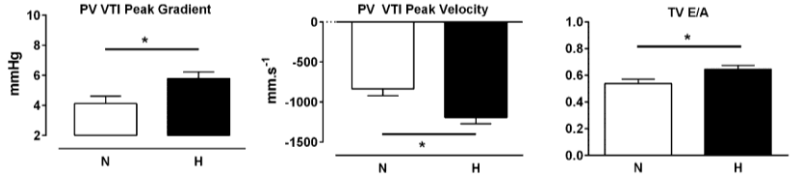
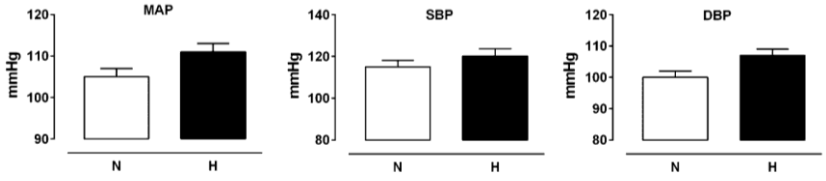
In 2016, Nicole was named as one of the top Italian women scientists by the Italian National Observatory on Women's Health. Her research uses cutting-edge genomic analysis with deep clinical phenotyping to study how human genome variation influences the risk of common diseases – with an emphasis on cardio-metabolic disorders.

Nicole is a member of the Cambridge University Platelet Biology and Cardiovascular groups, the NIHR Blood and Transplant Research Unit in Donor Health and Genomics and the EU BLUEPRINT and EpiGeneSys projects. She serves in several steering committees, on the scientific advisory board of the GECCO Consortium, and is on the editorial board for the European Journal of Human Genetics, Genome Medicine, Trends in Genetics, Cardiogenetics and Molecular Biology and Evolution.

Talks

TITLE	**THE MITOCHONDRIAL-TARGETED ANTIOXIDANT MITOQ PREVENTS THE PROGRAMMING OF CARDIOVASCULAR DYSFUNCTION BY DEVELOPMENTAL HYPOXIA IN SHEEP**
AUTHOR(S)	Botting. K.J.[†*], Skeffington, K.L.[†], Niu, Y., Allison, B.J., Brain, K.L., Itani, N., Beck, C., Logan, A., Murray, AJ, Murphy, M.P. & Giussani, D.A. [†] *Co-first authors*
ABSTRACT	**Introduction:** Chronic fetal hypoxia programmes cardiovascular dysfunction via oxidative stress (1). In rodents, maternal treatment of hypoxic pregnancies with the antioxidant vitamin C is protective, however, only at concentration incompatible with human clinical translation (2,3). Here, we show in sheep that MitoQ is a suitable alternative therapeutic candidate. **Methods:** Singleton pregnant ewes with an indwelling femoral artery and vein catheter were exposed to normoxia (N) or hypoxia (H; 10% O_2) with or without maternal MitoQ treatment (Q; 1.2 mg/kg/day i.v. in saline) during the last third of gestation (105-138 days; *n*=7-10). Offspring were maintained until 9 months, and then chronically instrumented with vascular catheters and a femoral flow probe to determine *in vivo* cardiovascular function followed by *ex vivo* peripheral endothelial function (wire myography). Data were analysed by 2-way ANOVA with repeated measures, as appropriate. **Results**: Offspring of hypoxic pregnancy were smaller at birth (N:3.4±0.2; H:3.0±0.1; HQ:3.0±0.2; NQ:3.4±0.2kg, P<0.05) and hypertensive at adulthood (A). Maternal MitoQ in hypoxic pregnancy restored the programmed hypertension in adult offspring. Adult offspring from MitoQ pregnancies showed increased *in vivo* NO bioavailability evidenced by a greater fall in femoral vascular conductance to NO blockade with LNAME (100 mg/kg i.a.; B) and by *in vitro* restoration of the programmed impaired femoral artery dilator sensitivity to SNP (C). **Conclusions:** Maternal MitoQ treatment in pregnancy complicated by chronic fetal hypoxia protects against programmed cardiovascular dysfunction in adulthood. The mechanism underlying this protection involves programmed increases in NO bioavailability and sensitivity in the cardiovascular system of the adult offspring. 1. *Giussani & Davidge (2013). J Dev Orig Health Dis. 4(5), 328-37;* 2. *Giussani DA et al. (2012). PLoS One 7(2), e31017;* 3. *Kane AD et al. (2013). Circ J. 77(10), 2604-11*  **Figure 1.** Mean arterial pressure in adulthood (A), femoral vascular conductance in response to LNAME bolus (B) and *in vitro* femoral artery relaxation to increasing SNP concentration (C). P<0.05; 2-way ANOVA for effect of Hypoxia (*) and MitoQ (†).
THANKS	Supported by the *British Heart Foundation*

TITLE	**MATERNAL OVER-NUTRITION PROGRAMS VENTRICULAR REMODELLING AND CARDIAC DYSFUNCTION INDEPENDENTLY OF POST-NATAL DIET**
AUTHOR(S)	Elena Loche*, Heather L Blackmore, Asha M Carpenter, Denise Fernandez-Twinn, Jessica Beeson, Thomas Ashmore, Susan E Ozanne
ABSTRACT	**BACKGROUND** Gestational exposure to maternal obesity increases the risk of cardiovascular disease (CVD) in the offspring. **AIM** To characterize the consequences of a combinatorial exposure to maternal and post-weaning obesogenic diet on offspring cardiac structure and function. **METHODS** A well-established mouse model of maternal diet-induced obesity where C57bl/6 dams are fed a high fat/high simple carbohydrate diet was used. On postnatal day 21, male offspring from control (C-) and obese (O-) dams were weaned onto chow (-C) or the obesogenic diet (-O), generating 4 experimental groups: CC, CO, OC and OO. Cardiac structure and function were assessed by stereology and echocardiography. **RESULTS** Young adult (8 weeks) offspring exposed to over-nutrition during gestation and lactation had heavier hearts (17%) than control mice (effect of maternal diet p=0.005). A post-weaning obesogenic diet also increased heart weight (effect of offspring diet p= 0.019). OC and OO groups developed pathological ventricular remodelling associated with re-expression of cardiac fetal genes, interventricular septum thickening (p=0.0004) and increased left ventricular area (p=0.02). OC mice developed systolic dysfunction with reduced ejection fraction and fractional shortening (-23% and -33% vs CC, respectively); OO cardiac function was less impaired (-7% and -11%, respectively). Most importantly, up-regulation of genes involved in cardiac contraction was observed in fetuses from obese dams as early as *in utero*. **CONCLUSIONS** These findings suggest that a maternal obesogenic environment is a critical determinant of CVD risk in the next generation and has as big an effect on cardiac health as current obesity.
THANKS	We thank the British Heart Foundation and Medical Research Council for funding our research.

TITLE	**DEVELOPMENTAL PROGRAMMING OF PULMONARY HYPERTENSION BY CHRONIC PRENATAL HYPOXIA**
AUTHOR(S)	A.M. Spiroski*, C.J. Shaw, E.J. Camm, T.J., Ashmore, M.R. Sutherland, A.M. Nuzzo, E.R. Eastwell, & D.A. Giussani
ABSTRACT	**Introduction:** Late gestation hypoxia-induced intrauterine growth restriction (IUGR) is associated with left heart dysfunction in young adult rats and ageing-associated pulmonary hypertension (PHT). Whether chronic prenatal hypoxia programmes PHT in later life in the absence of IUGR is unknown. We hypothesised that chronic prenatal hypoxia would programme PHT in adulthood independent of IUGR. **Methods:** Pregnant Wistar dams were exposed to hypoxia (H; 13% O_2) or normoxia (N; 21% O_2) from 6-21 days gestation (term ~22 days). Offspring were maintained in normoxia to 4 months of age. One male per litter was selected for either echocardiography, performed under 10 mg▪kg^{-1} xylazine and 100 mg▪kg^{-1} ketamine (N: n=11, H: n=8), or conscious cardiovascular assessment. Femoral catheters were inserted under isoflurane anaesthesia and cardiovascular function was determined 4-5 days post-operatively (N: n=10, H: n=8). **Results**: Pulmonary valve velocity time interval (PV VTI) peak pressure (mmHg) and velocity (mm▪s^{-1}) were elevated and tricuspid valve E/A ratio (TV E/A) was greater in H vs. N offspring (Fig. 1A). The ratio of diastolic right ventricle to left ventricle internal diameter (RVIDd/LVIDd) relative to bodyweight was greater in H compared with N offspring (0.42±0.01 *vs.* 0.36±0.03, $p<0.05$). M-Mode measurement of ejection fraction and pulse wave Doppler mitral E/A ratios were not different. Similarly, mean arterial (MAP), systolic and diastolic blood pressures (SBP and DBP, respectively) were not different (Fig. 1B). **Conclusions:** These data suggest that chronic prenatal hypoxia programmes PHT independent of IUGR and postnatal normoxia, prior to the development of significant left heart and systemic dysfunction. **A. Echocardiography**  **B. Arterial Blood Pressure**  **Figure 1. Cardiovascular Function.** Cardiovascular measures were analysed in normoxic (N, white) and hypoxic (H, black) offspring by *t*-test. Values are mean ± SEM; *$p<0.05$.
THANKS	*Supported by funding from the British Heart Foundation*

TITLE	**DURABILITY PREDICTION FOR THE DESIGN OF A NEW POLYMERIC HEART VALVE PROSTHESIS**
AUTHOR(S)	M. Serrani*, J. Brubert , J. Stasiak, F. De Gaetano, M.L. Costantino, G.D. Moggridge
ABSTRACT	In the development of a clinically viable polymeric heart valve prosthesis (PHV), the achievement of an adequate device lifetime remains one of the main challenges to solve. Our group has developed a new bio-inspired PHV made of a styrenic block copolymer. The mechanical properties of this polymer can be tuned via the manufacturing process to obtain an anisotropic mechanical behaviour, in fact mimicking the native tissue microstructure by orienting the polymer cylindrical micro-morphology. The aim of this work is to implement a modelling tool which, combined with experimental data on the polymer fatigue properties, will allow to predict the device lifetime in order to optimise the valve design. A finite element model of the polymeric valve was developed. The block copolymer mechanical behaviour was described by an anisotropic hyperelastic constitutive law; the material parameters were estimated by uniaxial tensile tests. A MATLAB routine was implemented to define the material orientation within the valve leaflets, based on experimental data of the material microstructure. Physiological pressure and boundary conditions were applied to simulate the valve closing. The simulations allowed to calculate the maximum Strain Energy Density (SED) in the valve for different designs and working conditions. In parallel, crack propagation tests were performed on polymeric samples to find the relationship between number of cycles to failure and SED for the material. The valve lifetime was then predicted by combining the modelling and experimental results. Therefore, this method can be used to optimise the PHV design in terms of durability.
THANKS	The authors thank the British Heart Foundation for the financial support to this work under Grant Nos. NH/11/4/29059 and SP/15/5/31548.

ABSTRACT	**DESIGNING SCAFFOLD BIOMATERIALS FOR HEART TISSUE REPAIR**
AUTHOR(S)	V Graup*, S Best, R Farndale, T Krieg, S Sinha & R Cameron
ABSTRACT	With cardiovascular disease being the leading cause of death in the western world, research into treatment for post-myocardial infarct has steadily increased in recent decades. One possible approach to limit chronic tissue damage and promote healing is the application of cardiac patches. This approach investigates the use of porous collagen patches as cardiac patch material and therefore carrier material for drugs and stem cells *in vivo* and *in vitro*. After being generated, collagen scaffolds – like most polymers – are stabilised using crosslinking agents. The crosslinking procedure causes a depletion of potential cell binding sites within the scaffold, limiting its suitability. However, combining crosslinking with UV irradiation may allow these binding sites to be preserved and alter swelling and degradation behaviour of scaffolds in different areas of application. Our results indicate that UV irradiation has an effect upon scaffold properties in non-crosslinked scaffolds and in combination with low-level chemical crosslinking. It stabilises the scaffolds and increases their swelling capacity. Furthermore, it increases the compressive modulus in non-chemically cross-linked and slightly cross-linked scaffolds. In conclusion, UV irradiation can contribute favourably to scaffold stability while preserving binding sites for cell attachment normally lost during chemical crosslinking.
THANKS	*Supported by a special project grant from the British Heart Foundation*

TITLE	**CORRECTION OF MARFAN MUTATION C1242Y IN HUMAN IPS CELLS USING CRISPR/CAS9 TECHNOLOGY REESTABLISH NORMAL PHENOTYPE IN HUMAN NEURAL CREST-DERIVED SMOOTH MUSCLE CELLS**
AUTHOR(S)	Serrano F*, Granata A, Bernard WG, McNamara M, Low L, Sastry P, and Sinha S.
ABSTRACT	Marfan syndrome (MFS) is a heritable autosomal dominant disorder of connective tissue that affects 1 in 5,000 individuals worldwide. The principal cause of early mortality in Patients with MFS is the development of thoracic aortic aneurysm (TAA); a potentially devastating process that can progress to aortic dissection or rupture in the absence of symptoms. Mutations in the fibrillin-1 (FBN1) gene, which encodes a major constituent of microfibrils found in the extracellular matrix (ECM), cause MFS. Fibrillin-1 has been shown to interact with and control the bioavailability of TGF-□, a potent cytokine that regulates proliferation, differentiation, ECM modeling and apoptosis. Our MFS-hiPSC derived smooth muscle cells closely mimic the aortic phenotype of MFS patients and have allowed us to study the molecular mechanisms causing disease. To verify that the MFC1242Y hiPSC-derived SMC phenotype is caused solely by the C1242Y mutation, we generated a CRISPR/Cas9 isogenic MF hiPSC line where the mutation has been replaced with a WT allele (1242Y- >C). In parallel, we have generated an isogenic CRISPR/Cas9 MF hiPSC line where the mutation has been replaced with the mutant C1242Y allele as control (1242Y->Y). Corrected MF lines (1242Y->C) showed a WT fibrillin-1 phenotype compared to the original disease line, MFC1242Y and the CRISPR control line, 1242Y->Y. In 1242Y->C corrected NCSMC, the phosphorylated levels of both canonical and non-canonical effectors of the TGF-□□pathway were lowered to levels comparable to WT. In addition, TGF-□□levels in the supernatant of 1242Y->C corrected NC-SMC were significantly reduced.
THANKS	

TITLE	**FOXO3A INDUCES VASCULAR SMOOTH MUSCLE CELL APOPTOSIS THROUGH MMP-13: IMPLICATIONS FOR ATHEROSCLEROTIC PLAQUE RUPTURE**
AUTHOR(S)	*A.Fellows, H. Yu, M. Bennett
ABSTRACT	**Rationale:** Vulnerable atherosclerotic plaques are characterised by increased apoptosis of vascular smooth muscle cells (VSMCs) within the fibrous cap. Our laboratory has shown that these VSMCs exhibit impaired inhibition of the pro-apoptotic transcription factor FOXO3a, and recent evidence from other groups suggests that matrix metalloproteinase-13 (MMP-13) is an important enzyme in promoting plaque rupture. We investigated a link between FOXO3a and MMP-13 to elucidate their roles in VSMC apoptosis and atherosclerosis. **Methods:** We generated a transgenic rat VSMC line overexpressing a chimaeric FOXO3a protein (FOXO3aA3ER) that was inducible by 4-hydroxytamoxifen (OHT) but not inhibited by Akt. **Results:** FOXO3aA3ER cells exhibited increased apoptosis after FOXO3a activation (5.1±0.6% vs. 26.8±7.7%) with simultaneous and significant transcriptional upregulation of *Mmp13* (663±22-fold). The *Mmp13* promoter contained a FOXO binding site, as demonstrated by luciferase reporter assay and ChIP. Western blotting showed increased expression and cleavage of MMP-13 protein after FOXO3a activation, with heightened MMP-13-induced proteolysis on gelatin zymography. Importantly, FOXO3a-mediated apoptosis was almost completely reversed by attenuating MMP-13 activity using siRNA knockdown (7.7±3.4% vs. 0.7±1.9%). Finally, activation of endogenous FOXO3a in human aortic VSMCs using the PI3K inhibitor LY-294002 also led to FOXO3a-dependent upregulation of MMP-13. **Conclusions:** We show that FOXO3a induces VSMC apoptosis predominantly via upregulation of MMP-13 and this mechanism may be a potent inducer of vulnerable plaques in atherosclerosis.
THANKS	British Heart Foundation

TITLE	**GENERATING AN INDUCIBLE HUMAN iPSC LINE TO PRODUCE MATURE MEGAKARYOCYTES *IN VITRO***
AUTHOR(S)	Dalby A*, Bertero A, Ortmann D, Pawlowski M, Kotter M, Moreau T, Ghevaert C.
ABSTRACT	There exists a need to produce platelets *in vitro* for use in transfusion medicine, due to increased platelet demands and short platelet shelf life. Our lab has developed a technique called forward programming[1], which uses human iPSCs (induced pluripotent stem cells), to generate megakaryocytes (MKs), the precursor cells to platelets. Forward programming produces a high yield of mature MKs, in minimal cytokine and serum-free conditions. A major limitation of the current technology is the reliance on lentiviral transduction of three key haematopoietic transcription factors (TFs), which drives an identity change in the iPSCs, pushing them towards the MK lineage. Our aim, to overcome this issue, was to generate a stable inducible, iPSC line to use in forward programming. Genome engineering techniques have enabled us to insert the three TFs into the genome of iPSCs. Using an optimised Tet-on system, the TFs can be switched on at any desired time, to induce forward programming and produce mature megakaryocytes in just 20 days. Data from multiple clones, of two individual iPSC lines, shows that inducible forward programming is an efficient method for producing mature MKs. Removing the requirement of lentiviral transduction is a major advancement in forward programming that will make it more amenable to scaling-up, thus moving this technology closer towards our goal of producing *in vitro* platelets for use in transfusion medicine. [1]Moreau T *et al*. Large-scale production of megakaryocytes from human pluripotent stem cells by chemically defined forward programming. *Nat. Commun.* 7, 11208 (2016).
THANKS	

TITLE	**DEVELOPMENT OF INDUCED PLURIPOTENT STEM CELL MODELS OF PULMONARY ARTERIAL HYPERTENSION**
AUTHOR(S)	F. N. Kiskin*, C. J. Z. Huang, C-H Chang, E. M. Callery, T. Walsh, V. George, L. A. Hurst, A. Chida, S. Appleby, B. Kwieder, A. Beatie, M. Draper, M. Ellis, C. Denning, C. Cheung, S. Sinha , N. W. Morrell and A. A. Rana
ABSTRACT	Pulmonary arterial hypertension (PAH) is a debilitating and often fatal disease associated with reduced BMPR2 signalling. Limited human tissue is available for study and usually only from patients with end-stage disease, making it difficult to understand how PAH is established and progresses. Furthermore, BMPR2 knockout mouse models are unable to recapitulate the full repertoire of phenotypes observed in humans. We therefore require alternative human models of PAH. We derived iPSCs from patients with BMPR2 mutations and used CRISPR-Cas9 gene editing to introduce two specific BMPR2 mutations into control iPSCs with no history of PAH. Using these cells, we present the first human iPSC model of PAH involving the analysis of lineage-specific iPSC-derived pulmonary artery smooth muscle cell-like and arterial endothelial cell-like cells which recapitulate several PAH-associated phenotypes such as reduced Smad signalling, altered proliferation and apoptosis rates, and impaired vascular network assembly. These unique models with isogenic backgrounds reveal that a single *BMPR2* mutation is sufficient to cause many PAH-associated phenotypes, but that other factors may be necessary to enhance BMPR2-associated phenotypes *in vivo*. For example, we show that acquisition of the mitochondrial hyperpolarisation phenotype is enhanced by inflammatory signalling and requires an interaction between *BMPR2* mutations and environmental stimuli provided by exposure to serum over time. Taken together, the iPSC model provides a pre-disease state which can be transitioned into a diseased state, thus making it useful for identifying factors involved in disease penetrance and for validating therapeutic approaches that target *BMPR2*.
THANKS	We thank Dr Paul Upton and Dr Ian Horan for their help and support, and the British Heart Foundation for funding this project.

TITLE	**MODELLING SEASONAL AND SPATIO-TEMPORAL VARIATION: THE EXAMPLE OF RESPIRATORY PRESCRIBING**
AUTHOR(S)	E Sofianopoulou*, T Pless-Mulloli, S Rushton, PJ Diggle
ABSTRACT	Many measures of chronic diseases including respiratory disease exhibit seasonal variation together with residual correlation between consecutive time-periods and neighbouring areas. We demonstrate a strategy for modelling data that exhibit both seasonal trend and spatio-temporal correlation, through an application to respiratory prescribing. We estimated the seasonal pattern of prescribing by fitting a dynamic harmonic regression (DHR) model to salbutamol prescribing in relation to temperature. We compared the output of DHR models to static sinusoidal regression models. We used the DHR fitted values as an offset in mixed-effects models that aimed to account for the remaining spatio-temporal variation in prescribing rates. As diagnostic checks, we assessed spatial and temporal correlation separately and jointly. Our application of a DHR model resulted in a better fit to the seasonal variation of prescribing, than was obtained with a static model. After adjusting the final model for the fitted values from the DHR model, we did not detect any remaining spatio-temporal correlation in the model's residuals. Using a DHR model and temperature data to account for the periodicity of prescribing proved an efficient way to capture its seasonal variation. The diagnostic procedures indicated that there was no need to model any remaining correlation explicitly.
THANKS	We would like to thank Colt Foundation, UK Medical Research Council (G0800270), British Heart Foundation (SP/09/002), and UK National Institute for Health Research (Cambridge Biomedical Research Centre) for funding this research.

TITLE	**STRUCTURAL AND FLOW-DIVERTING EFFECTS OF MULTIPLE OVERLAPPING UNCOVERED STENTS: A NOVEL MANAGEMENT STRATEGY FOR THORACOABDOMINAL AORTIC ANEURYSM**
AUTHOR(S)	Shuo Wang*, Yongxue Zhang, Yuan Huang, Jiaxuan Feng, Jonathan H Gillard, Qingsheng Lu, Zhongzhao Teng
ABSTRACT	**Background**: Standard endovascular aortic repair (EVAR) with stent-graft is not suitable for treating complicated thoracoabdominal aortic aneurysms (TAAA) involving vital branches. Multiple uncovered stents (MOUS) were proposed to overcome this limitation by modulating the blood flow promoting thromblisation in the sac. Although the initial clinical experience was encouraging, the impact of overlapping pattern on structural and hemodynamic effects has not been studied. **Method**: A patient-specific TAAA model was reconstructed from contrast enhanced CTA images. Stent deployment and subsequent flow-diverting effects were simulated using finite element analysis (FEA) and computational fluid dynamic (CFD) analysis. Structural stress concentration within vessel wall and flow variables were quantified. Parameter studies by changing the circumferential and axial overlapping patterns were performed to assess effects of different 2-stent deployments. **Results**: In total, 18 different overlapping patterns were simulated, including 9 different circumferential angles and 9 different axial displacements. The structural stress in the landing zone increased with the number of deployed stents while the sac wall-averaged stress value remained unchanged. Structural stress level was not effected by different overlapping patterns. Sac-averaged flow velocity and wall shear stress decreased significantly while oscillatory shear index and relative residence time increased with the number of deployed stents. Less modulating effects were seen when the deployments of 2 stents were exactly matched compared to other overlapping patterns. **Conclusion**: High stress concentration in the landing zone increased and aneurysmal sac flow velocity decreased significantly after 2 stents deployment. Except for the perfect match, different 2-stent overlapping pattern has little effect on haemodynamic parameter calculations.
THANKS	This study is support by National Nature Science Foundation of China (81170291, 39800177, and 30772140) and Chinese Scholarship Council.

TITLE	**NON-INVASIVE IDENTIFICATION OF CULPRIT CAROTID ATHEROMA USING SODIUM FLUORIDE-POSITRON EMISSION TOMOGRAPHY**
AUTHOR(S)	NR Evans*, JM Tarkin, MM Chowdhury, S Malani, JHF Rudd, EA Warburton
ABSTRACT	**Introduction:** Microcalcification is a histopathological feature of atheroma at risk of rupture; so-called "vulnerable plaques." Positron emission tomography (PET) using ^{18}F-sodium fluoride (NaF) has been used to detect microcalcification in *ex vivo* histology, though its use *in vivo* has been limited. We investigated the utility of NaF-PET to identify culprit carotid artery atheroma non-invasively *in vivo* in the setting of acute ischemic stroke. **Methods:** Symptomatic carotid artery stenosis of $\geq$50% was imaged using NaF-PET within 14 days of ipsilateral ischemic stroke. Symptomatic arteries were compared to contralateral asymptomatic carotid arteries. NaF dose was 125 MBq with 60 minute uptake on a GE Discovery 690 with 64 slice computed tomography. NaF uptake was measured using standardized uptake values for each artery's single region of maximum uptake (SUVmax) and the mean of the three slices representing the most diseased segment (MDS-SUVmax). **Results:** Fifty-two carotid arteries were analyzed: 26 symptomatic, 26 asymptomatic. Median SUVmax was higher in symptomatic than asymptomatic arteries: 2.16 (IQR 0.76) and 1.88 (IQR 0.94) respectively ($p<0.001$). MDS-SUVmax was 2.04 (IQR 0.66) in symptomatic and 1.76 (IQR 0.83) in asymptomatic carotids ($p<0.001$). Calcium scores did not differ between symptomatic and asymptomatic arteries ($p=0.34$). **Conclusions:** The ability to identify culprit carotid atheroma using NaF-PET *in vivo* represents an important advance in vascular imaging. This has important implications for understanding atherosclerosis pathophysiology, as well as potential clinical applications to identify and risk-stratify vulnerable carotid atheroma.
THANKS	

Posters

TITLE	**MODELLING INTRACELLULAR ZINC RELEASE IN PLATELETS**
AUTHOR(S)	Ahmed NS* and Pugh N
ABSTRACT	**Introduction:** Elevation of intracellular calcium (Ca^{2+}), driven by store release is a hallmark of platelet activation. Zinc (Zn^{2+}) has been shown to be released from intracellular compartments of a variety of cell types in response to external stimuli. However, the role of Zn^{2+} release in platelets has yet to be determined. Ionophores facilitate rapid equilibration of ionic species across membranes, and are frequently used to mimic intracellular ion release. Here we employed zinc-specific ionophores to examine the effect of increased intracellular Zn^{2+} concentration on platelet physiology. **Methods:** Platelet activation in response to the Zn^{2+}-specific ionophores, clioquinol and pyrithione, were assessed using washed platelet suspensions by light transmission aggregometry. Where stated, platelets were pre-incubated with a panel of inhibitors prior to addition of ionophores. Platelet shape change and aggregation were visualized using confocal microscopy. Changes of intraplatelet Zn^{2+} were assessed by flow cytometry. **Results:** Treatment of platelet suspensions with Zn^{2+} ionophores led to platelet activation. Clioquinol induced platelet shape change followed by submaximal aggregation, whilst pyrithione caused significant platelet shape change without aggregation. Pre-treatment of platelets with the Zn^{2+} chelator, TPEN reduced the effects of Zn^{2+} ionophores. Cytochalasin-D significantly reduced Zn^{2+}-ionophore-induced shape change. **Conclusion:** These data constitute the first report of platelet activation in response to Zn^{2+}-specific ionophores. Platelet stimulation by clioquinol and pyrithione was accompanied by a substantial shape change. Experiments conducted in the presence of cytochalasin-D indicate a role for Zn^{2+} in the modulation of cytoskeletal rearrangements. It will therefore be important to consider the role of intracellular Zn^{2+} during platelet activation.
THANKS	Special thanks to my supervisor Dr. Nicholas Pugh and Dr. Kirk Taylor

TITLE	**DIRECT EFFECTS OF PRAVASTATIN OR MELATONIN ON CARDIOVASCULAR FUNCTION IN THE CHRONICALLY-HYPOXIC FETUS: A COMPARISON OF TWO ANTIOXIDANT STRATEGIES**
AUTHOR(S)	N Itani*, KL Skeffington, Y Niu, C Beck, and DA Giussani
ABSTRACT	Maternal treatment with either pravastatin or melatonin to protect growth in the hypoxic fetus in complicated pregnancy is currently undergoing multicentre human clinical trials. However, whether these treatments have additional beneficial or detrimental effects on the hypoxic fetus is completely unknown. The chick embryo is the only established animal model to isolate the direct effects of any therapy on the fetus independent of the maternal or placental physiology. Therefore, this study investigated the effects on cardiac and vascular function of treatment with either pravastatin or melatonin in the hypoxic chick embryo. Fertilised eggs (n=7-10 per group) were incubated under normoxia (N) or hypoxia (H, 14%) from day 1 (term: 21 days). Pravastatin (1mg.kg^{-1}), Melatonin (1mg.kg^{-1}) or vehicle was injected daily into the air cell from day 13 of incubation, which equates to 25 weeks of human pregnancy. At day 19, the embryo was euthanized and cardiovascular function was determined using a Langendorff preparation and a wire myograph. Chronic fetal hypoxia impaired systolic (reduced left ventricular developed pressure, LVDP) and diastolic (elevated LV end diastolic pressure, LVEDP) function (Fig. 1). While treatment with melatonin rescued systolic function, pravastatin rescued diastolic function in hypoxic embryos. Chronic hypoxia induced endothelial dysfunction in femoral vessels (N: 7.0±0.1 and H: 6.3±0.1, sensitivity [pD2] to log [acetylcholine], $P<0.05$). Treatment with melatonin or pravastatin rescued endothelial function in hypoxic embryos (HM: 7.0±0.1, HP: 7.0±0.2). We show that human clinically-relevant doses of antioxidants also have direct beneficial effects on the developing cardiovascular system of the hypoxic fetus.
THANKS	British Heart Foundation

TITLE	**PROBING THE EFFECT OF FREE FATTY ACIDS ON PLATELET ACTIVATION *IN VITRO***
AUTHOR(S)	Janay Gibbons, Kirk A. Taylor, Linda King and Nicholas Pugh*
ABSTRACT	**Introduction:** Free fatty acids (FFAs) are present in atherosclerotic plaques and are elevated in the plasma of obese and diabetic patients. Liberation of FFAs upon plaque rupture may contribute to thrombosis. The effect of FFAs on platelet behaviour is controversial. Here, we investigated the effect(s) of physiologically abundant FFAs, palmitic acid (PA) and oleic acid (OA) on platelet activation. **Methods:** PA and OA were homogenised in 100% methanol. Platelet responses to PA or OA were assessed by light transmission aggregometry, flow cytometry and Western blotting. FFA-induced signalling was assessed using a panel of inhibitors. Platelet aggregates were visualised by confocal microscopy. FFA-induced tyrosine phosphorylation of platelet proteins was assessed by Western blotting. **Results:** Treatment with OA, but not PA, induced changes in light transmission that were consistent with platelet aggregation, the extent and rate of which was comparable to that of conventional platelet agonists. OA-induced aggregation was resistant to a panel of antagonists, indicating a role for agglutination. However, formalin fixation of platelets abolished OA-induced responses. OA-induced treatment was accompanied by tyrosine phosphorylation of platelet proteins. Granule release and integrin $\alpha_{IIb}\beta_3$ activation were not detected. **Conclusions:** These data indicate that OA, but not PA, initiates a platelet response that is consistent with agglutination. However, changes in tyrosine phosphorylation and a lack of response to OA by formaldehyde fixed platelets suggests the activation of intracellular signalling mechanisms. These findings suggest a novel mechanism by which platelets contribute to thrombus formation at sites of atherosclerotic plaque rupture.
THANKS	This work is supported by a BHF project grant (PG/14/47/30912)

TITLE	**CARDIAC ACTION OF THE FIRST G PROTEIN BIASED SMALL MOLECULE APELIN AGONIST**
AUTHOR(S)	C Read*, C Fitzpatrick, P Yang, R. E. Kuc, J.J. Maguire, R Glen, R Foster, A.P. Davenport
ABSTRACT	Pulmonary arterial hypertension (PAH) has a poor prognosis and is associated with pulmonary vasoconstriction, right ventricular hypertrophy and right heart failure. Current therapies aim to reduce vasoconstriction but do not benefit the heart and more efficacious treatments are required. Apelin produces vasodilatation and cardiac inotropy, while its expression is decreased in PAH. The apelin receptor is present and apelin infusion is beneficial in animal models. Apelin lacks bioavailability, is limited by half-life and induces rapid internalisation of the receptor through β-arrestin signalling. G protein biased small molecule agonists could produce vasodilatation and protect against remodelling of the right ventricle without receptor desensitisation. We have identified a small molecule, CMF-019, which bound to human, rat and mouse apelin receptors with nanomolar affinity in heart homogenates (pK_i=8.58±0.04, 8.49±0.04 and 8.71±0.06 respectively). In cell-based functional assays, whereas CMF-019 showed similar potency for the $G_{\alpha i}$ pathway to apelin (pD_2=10.00±0.13 vs pD_2=9.34±0.15 respectively), in β-arrestin (pD_2=6.65±0.15 vs pD_2=8.65±0.10) and internalisation (pD_2=6.16±0.21 vs pD_2=9.28±0.10) assays it was much less potent. CMF-019 displayed a bias of ~400 in cAMP over β-arrestin signalling and ~6000 over internalisation. CMF-019 (5000nmol) intravenously injected into male Sprague-Dawley rats (273±6g) significant increased cardiac contractility (dP/dt_{Max}, 833±152mmHg/s) compared to saline (88.7±94.4mmHg/s) ($p<0.001$, student's t-test). CMF-019 is the first biased small molecule identified at the apelin receptor and displays activity *in vivo*. It illustrates that biased agonism can be retained in small molecules and provides a basis for the rational design of new biased apelin mimetics for PAH treatment.
THANKS	

TITLE	**RBPMS: A NEW PLAYER IN THE ALTERNATIVE SPLICING PROGRAM OF VASCULAR SMOOTH MUSCLE CELLS**
AUTHOR(S)	Nakagaki Silva E. E.*, Smith C. W. J.
ABSTRACT	Vascular smooth muscle cells (VSMCs) present phenotypic diversity and plasticity and despite the importance of alternative splicing (AS) in proteome expansion and gene expression regulation, studies elucidating the importance of AS in VSMC are still limited. We set out to identify tissue-specific "splicing master" regulators of VSMCs, by identifying RNA binding protein (RBP) genes associated with superenhancers. RBPMS is an RBP with no described splicing function, which was found to be associated with SMC superenhancers and highly expressed in VSMCs. We investigated the role of RBPMS in VSMC by overexpression and knockdown of its isoforms in PAC-1 and HEK293, looking for changes in the AS pattern of reporters and endogenous splicing events by RT-PCRs. RBPMS was found to exist in several isoforms and showed predominantly nuclear localization in PAC-1 cells, with some cytoplasmic localization. RBPMS overexpression promoted the SMC-specific splicing patterns of exons in the Tpm1, Actn1, Myocd and FLNB genes. Only one of the RBPMS isoforms was able to promote exon skipping (of Tpm1 and Actn1), but all isoforms could promote exon inclusion (of Myocd and FLNB). RBPMS knockdown also revealed alterations in the AS program of PAC1 SMCs. Finally, deletion of the known RBPMS binding sites, CAC motifs, downstream of the Myocd exon 2a impaired the ability of RBPMS to promote exon 2a inclusion. In summary, RBPMS affects AS of many SMC genes. Consistent with the hypothesis that RBPMS might be a VSMC post-transcriptional master regulator, inclusion of Myocardin exon 2a is known to promote VSMC differentiation.
THANKS	CNPq, Wellcome Trust

TITLE	**INTERPLAY BETWEEN CALCIUM AND ZINC: IMPLICATIONS FOR PLATELET ACTIVATION**
AUTHOR(S)	Taylor, K.A.* and Pugh, N.
ABSTRACT	Dietary zinc (Zn^{2+}) deficiency causes a bleeding phenotype in humans and rodents. Zn^{2+} is released and concentrated at sites of vascular injury and has been shown to directly activate platelets, however the underlying mechanism(s) remains unclear. In this study we investigate potential routes for platelet Zn^{2+} entry using channel blockers and Zn^{2+}-sensitive FluoZin-3 dye. Furthermore we monitored fluctuations of intracellular Ca^{2+} and expression of platelet activation markers in the presence of Zn^{2+}. The sodium/calcium exchanger (NCX) and members of the transient receptor potential (TRP) channel family have previously been shown to conduct Zn^{2+}. Therefore, contributions by these channels to Zn^{2+}-induced aggregation was assessed in the presence of a panel of channel blockers. A number of compounds inhibited Zn^{2+}-induced aggregation with IC_{50} values ranging from 23-78 μM. Co-application of TRP and NCX blockers abrogated Zn^{2+}-induced aggregation. Further studies demonstrated reduced aggregation responses to CRP and thrombin in the presence of these drugs. We therefore assessed the impact of Zn^{2+} on CRP- and thrombin-induced calcium (Ca^{2+}) responses. Pre-incubation of platelets with sub-activatory Zn^{2+} (30 μM) reduced Ca^{2+} responses, without altering the expression of platelet activation markers. These data demonstrate a role for TRP channels and NCX in coordinating the platelet response to Zn^{2+}. Low concentrations of Zn^{2+} reduced agonist-induced Ca^{2+} responses, likely via reduction of Ca^{2+} release from the intracellular store. Given that the expression of activation markers was not affected by Zn^{2+}, these data further support a potentiatory role for Zn^{2+} during platelet activation.
THANKS	This work was funded by the British Heart Foundation

TITLE	**FUNCTIONAL CHARACTERISATION OF SMIM1 DURING MEGAKARYOPOIESIS AND ERYTHROPOIESIS**
AUTHOR(S)	A.R. Tomé *, S. Farrow, R. Petersen, I. Rosa, T. Bariana, F. Burden, K. Rehnstrom, W. H. Ouwehand and M. Frontini
ABSTRACT	Vel is a universal antigen present on red blood cells (RBCs) membrane, which defines the Vel-blood group. Population studies have shown a frequency of ~1/4000 Vel-negative individual in Europe[1]. *SMIM1* is a recently identified gene, underlying the Vel-antigen. It is a novel regulator of erythropoiesis and megakaryopoiesis and it is likely part of a membrane multi-protein complex. Previous observations in Zebrafish knockdown for *smim1* and gene expression data of different blood cell progenitors and precursors highlighted that *SMIM1* is not only important in RBCs biology but also in the specification of the cell fate at megakaryocyte erythrocyte progenitor (MEP)[1]. Moreover, a genome wide association study in human RBCs described a SNP (rs1175550) in the *SMIM1* gene as regulator of mean cell haemoglobin concentration[2], which suggests a possible implication of *SMIM1* in iron homeostasis. My PhD project aims to identify possible partners of SMIM1 multi-protein complex and to obtain a detailed understanding of the mechanism(s) by which *SMIM1* plays a role in fate commitment at MEP stage and in iron uptake. These questions will be addressed using induced pluripotent stem cells (iPSCs) derived from Vel-negative donors; *SMIM1* knockout iPSCs generated using CRISPR/Cas9n; *SMIM1* knockout mice and analysis of blood parameters of Vel-negative donors. Preliminary results demonstrated that Vel-negative blood donors do not have a striking phenotype in RBCs and platelets formation, and iron metabolism. Furthermore, *SMIM1* is expressed at protein level in RBCs, megakaryocytes (MKs) and platelets but remarkably SMIM1 membrane---expression is not detected in MKs and platelets. 1. Cvejic, A., *et al*. (2013) Nat Genet. 45:5; 2. van der Harst, P. *et al*., (2012) Nature, 492:7429.
THANKS	We thank the Vel-negative donors who participated in this study, the NIHR Cambridge Biomedical Research Centre (BRC) – Human Induced Pluripotent Stem Cells core facility for generating iPSC from Vel-negative donors, Prof Wendy Erber for her expertise in blood cell morphology analysis and the Sanger Mouse genetics project for generating Smim1 knockout mice. Thanks are also extended to past and present members of Dr Mattia Frontini's team (Prof Ouwehand's group) and Cedric Ghevaert's group for practical assistance in the different experiments. ART is recipient of a PhD fellowship award from the Landsteiner Foundation for Blood Transfusion Research and research in the Prof Ouwehand's group is supported by the NHS Blood and Transplant, NIHR, British Heart Foundation, European Commission, MRC, and Wellcome Trust.

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Notes