



Clinical Academics in Training Annual Conference 2018

Thursday 8 November

Royal College of Physicians Edinburgh

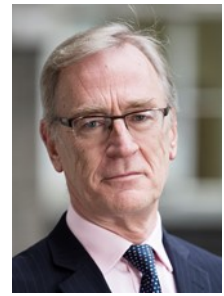
Abstract booklet

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Welcome to CATAC 2018

I am delighted to welcome you all to the debut Clinical Academics in Training Annual Conference 2018, as the Academy undertakes a shift to host its annual clinical meeting outside of London. I am looking forward to observing the increased diversity of talent that comes with a broader geographical remit, in addition to showcasing the incredible breadth of work that the Academy undertakes with a wider pool of researchers.



Please support me to extend my utmost gratitude to Professor Derek Bell and the Royal College of Physicians Edinburgh for generously hosting what is sure to be a fascinating meeting. I urge you all to learn more about the Academy and to take full advantage of this opportunity; meet fellow researchers across all career stages, learn about cutting edge research within academic medicine, and share your own research with the wider community.

Professor Sir Robert Lechler PMedSci, Vice Principal (Health) at King's College London, and Executive Director of King's Health Partners

This year's conference will be hosted at the Royal College of Physicians Edinburgh following the generosity of the President, Professor Derek Bell OBE RCPE. Not only is this an opportunity to showcase the newly refurbished venue, but also to celebrate and share the rich environment for medical research in Scotland.

'The Royal College of Physicians of Edinburgh look forward to welcoming the Clinical Academics in Training Annual Conference 2018 to Edinburgh. This event aligns with the priorities of the College, one of which is to support research through a variety of channels and to develop the researchers of the future. Since 2016 the College's own annual research symposium offers medical students and doctors in training an early opportunity to present findings, have early career research published and to build their networks.'



'We look forward to working with the Academy of Medical Sciences to host this prestigious event in Edinburgh on its first rotation from London, and we are proud that this event will be one of the first to be held in the College's new conference centre, which has just reopened after a multi-million pound refurbishment.'

Professor Derek Bell OBE FRCPE, President, Royal College of Physicians Edinburgh

The Academy of Medical Sciences' Regional Champion for Scotland Professor Jane Norman FMedSci has been influential in delivering the Academy's first CATAC meeting in Scotland.

'I am delighted to be part of this prestigious event. As the Academy of Medical Sciences' Regional Champion for Scotland, and chair of the CATAC 2018 Steering Committee, I have had the honour of selecting the abstracts that make up today's fantastic programme. The standard of abstracts received was exceptionally high and it was certainly a tough job to narrow them down. This high standard has really illustrated the value of hosting this meeting outside of London, and I look forward to learning of some of the great research that is being done.'



'I'd like to encourage fellows and junior colleagues present to really get involved, make new connections and to learn something new.'

Professor Jane Norman FMedSci, Professor of Maternal and Fetal Health, Director of the Tommy's Centre for Maternal and Fetal Health, Vice Principal, People and Culture, University of Edinburgh.

Networking activity

CATAC is a great opportunity for you to make some valuable connections with researchers spanning all career stages and specialities. To help you to maximise this opportunity, we have put together a series of networking checkpoints.

During the day try to speak to:

A Fellow of the Academy of Medical Sciences	
A researcher who is delivering an oral presentation	
A researcher who is delivering a poster presentation. Asking somebody about their poster is a great way to strike up a conversation.	
Someone from a different institution	
Someone who works in a different research field	
Someone who is at a different career stage	
Someone new from your host institution	
Someone with industry connections	

Useful information

Rooms in use:

Auditorium - presentations

Great Hall - multimorbidity session & drinks

Foyer area - posters & breaks

New Library - industry session

Wellbeing room - nursing room*

Vice President's office - prayer room*

**Please respect others' privacy and knock before entering*

Join in on social media:

Twitter

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[Academy of Medical Sciences](#)

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#CATAC2018

Programme

09:00	Registration and poster setup	Foyer Area
09:30	Welcome Professor Sir Robert Lechler PMedSci and Professor Derek Bell OBE FRCPE	Auditorium
09:45	Adventures in academia: from womb to tomb Dr Katherine Sleeman, King's College London	Auditorium
10:30	Poster Competition <i>Join a group to hear two minute presentations from clinical academics working in one of four broad research categories:</i> Group A - Applied health services research; Epidemiology; Population health sciences Group B - Cellular and molecular biology; Genetics Group C - Inflammation; Infection; Immunity Group D - Neurology; Neuroscience; Imaging; Technology	Foyer Area
11:30	Refreshment break	Foyer Area
12:00	Pre-Doctoral Plenary Competition <i>Each competitor will have five minutes to present their research:</i> 'Forced expression of retinoic acid receptor alpha potentiates differentiation of acute myeloid leukaemia' Dr Duncan Brian, University College London 'Rare variants in Steroid Receptor Coactivator 1 (SRC-1) associated with severe obesity' Dr Tessa Cacciottolo, University of Cambridge 'Identifying biological pathways to Alzheimer's Disease using MRI markers and polygenic scores: a cross-sectional study' Dr Judith Harrison, Cardiff University 'Obstructive sleep apnoea is associated with activation of the hypothalamic pituitary adrenal axis but antagonism of the glucocorticoid receptor is unlikely to prevent the associated metabolic disease' Dr Jonathan Hazlehurst, University of Birmingham 'Circadian regulation of macrophage phagocytosis is mediated by a REV-ERBa independent BMAL1/RhoA pathway' Dr Gareth Kitchen, University of Manchester 'Altered vascular function in boys with hypospadias- role of reactive oxygen species' Dr Angela Lucas-Herald, University of Glasgow 'The impact of the SIGN head injury guidelines and NHS 4-hour Emergency Target on hospital admissions for head injury in Scotland: An Interrupted Times Series' Dr Carl Marincowitz, Hull York Medical School 'Gestational age at delivery of twins and the risk of perinatal death: a Scottish population based cohort study' Dr Sarah Murray, University of Edinburgh	Auditorium

An introduction to our speakers

Keynote speakers

Adventures in academia: from womb to tomb

Dr Katherine Sleeman

NIHR Clinician Scientist and Honorary Consultant in palliative medicine
King's College London



I am a clinician and academic in palliative medicine at the Cicely Saunders Institute, King's College London. My path to academic palliative medicine was a meandering one, along which I picked up a BSc in developmental biology and a PhD in stem cell biology. In 2010 I was appointed to an NIHR Clinical Lectureship in palliative medicine at King's College London, and since 2016 I have held an NIHR Clinician Scientist fellowship. My research focus is on the use of routinely collected clinical and administrative data to understand and improve end of life care, particularly for people with dementia. I am also interested in public and policy engagement around end of life care. I live in London and have two sons. I am on Twitter [@kesleeman](https://twitter.com/kesleeman).

Life on the moon – my career in industry and academia

Professor Ed Bullmore FMedSci

Professor of Psychiatry
University of Cambridge



Ed Bullmore trained in clinical medicine at the University of Oxford and St Bartholomew's Hospital in London, then worked as a Lecturer in Medicine at the University of Hong Kong, before specialist clinical training in psychiatry at St George's Hospital, and then the Bethlem Royal & Maudsley Hospital, in London. His research career started in the early 1990s as a Wellcome Trust (Advanced) Research Fellow and was initially focused on mathematical analysis of neurophysiological time series. Since moving to Cambridge as Professor of Psychiatry in 1999, his interest in human brain function and structure has increasingly focused on complex brain networks identified in MRI and other brain scanning data. Since 2005, he has worked half-time for GlaxoSmithKline first as Head of GSK's Clinical Unit in Cambridge and since 2013 as Vice-President, Experimental Medicine in ImmunoPsychiatry. He is Clinical Director of the Wellcome Trust/MRC funded Behavioural & Clinical Neuroscience Institute, Scientific Director of the Wolfson Brain Imaging Centre, and Co-Chair of Cambridge Neuroscience, in the University of Cambridge; and an honorary Consultant Psychiatrist and Director of R&D in Cambridgeshire & Peterborough Foundation NHS Trust.

Since October 2014 he has been Head of the Department of Psychiatry at the University of Cambridge. He has published about 400 scientific papers with an h-index (Scopus) of 101. He has been elected as a Fellow of the Royal College of Physicians, the Royal College of Psychiatrists, and the Academy of Medical Sciences.

Opportunities to address multimorbidity

Dr Rachel Brown

Dr Rachel Brown is a senior policy officer at the Academy of Medical Sciences where she provides overall support to Academy's international portfolio. In this role, she has acted as lead Secretariat for the Academy's first international working group project - '*Multimorbidity: a priority for global health research*', the report of which was published in April 2018 and has since been followed by an international workshop on UK and LMIC focused research priorities. Prior to joining the Academy, Rachel completed her PhD at University College London.



Dr Lynne Corner



Dr Lynne Corner is Director of VOICE, an international organisation established in 2007 and based at the National Innovation Centre for Ageing at Newcastle University. VOICE aims to harness the immense experience, ideas and insights of the public, especially older people, to develop evidence based products and services that are needed to support healthy ageing, working with researchers and businesses, and to respond to the challenges and opportunities arising from demographic change.

Dr Corner is also Director of Engagement at the Newcastle University Institute for Ageing. She works closely with the NIHR Innovation Observatory on the Horizon Scanning and public insights programme, and co leads the NIHR James Lind Alliance Priority Setting Partnership on older people living with multiple conditions.

Lynne has a special interest in dementia, and through the Dementia Innovation Hub at Newcastle University works with families living with dementia to develop training and support to help people live well with dementia.

Professor Bruce Guthrie

Professor Bruce Guthrie is a health services researcher using mixed quantitative and qualitative methods to understand and improve the quality and safety of healthcare. His research is focused on multimorbidity, polypharmacy and prescribing quality and safety. He leads a number of projects in this field, and additionally collaborates with colleagues in the UK and internationally.

Professor Guthrie's research spans the range from basic epidemiology and qualitative research, through pragmatic randomised trials of organisational interventions, to applied work with the NHS to translate research findings into real-world improvements in the quality and safety of healthcare.



In multimorbidity, his research includes epidemiology (Lancet. 2012;380:37-43; BMC Medicine. 2015;13:74) intervention development and evaluation (BMC Medicine. 2016;14(1):1-10; Lancet. 2018;392(10141):41-50), and work on how guidelines could better account for multimorbidity (BMJ. 2012;345:e6341). To ensure the implementation of research findings in the NHS, Professor Guthrie has served on a number of national committees including being the chair of the Guideline Development Group for the NICE Multimorbidity clinical guideline published in 2016, and a member of the Academy of Medical Sciences multimorbidity working group.

Professor Frances Mair

Professor Frances Mair is a University of Glasgow medical graduate who undertook her vocational training in General Practice in Glasgow. She then went on to work as General Practitioner/Quality Assurance Physician Advisor for the US Navy/US Embassy, London, UK and subsequently entered academic general practice at the University of Liverpool where she became Professor of Primary Care Research and Director of the Mersey Primary Care R&D Consortium. While in Liverpool she had a one year research fellowship in Telemedicine/Family Medicine at the University of Kansas Medical Centre, USA. Professor Mair commenced at the University of Glasgow in 2005, was appointed Head of General Practice and Primary Care in 2009, and then appointed as Norie Miller Chair in General Practice in 2017 – the first female holder of this prestigious Chair.



Professor Mair is currently a visiting Professor at the Universities of Liverpool and Southampton. She is also a member of the MRC Clinical Research Training Fellowship panel. She was previously the former President of the Royal Society of Medicine, London, Telemedicine and E-Health Section and Associate Editor Journal of Telemedicine and Telecare. She was awarded the Society of Academic Primary Care and North American Primary Care Research Group Senior Investigator Award 2016.

Follow Frances Mair on Twitter: [@FrancesMair](https://twitter.com/FrancesMair)

Dr David McAllister



Dr David McAllister is a Senior Clinical Lecturer and Honorary Consultant (Public Health) at The University of Glasgow. In 2002, David graduated from medical school at the University of Glasgow, after which he worked in hospital medicine in Glasgow until 2007. He then undertook his doctoral research, funded via a personal fellowship with Chest, Heart and Stroke Scotland, at the University of Edinburgh and Columbia University in the City of New York, where he obtained advanced-level training in epidemiology.

In 2011 David moved specialty from respiratory medicine to public health medicine, and took up a post as a Clinical Lecturer in Epidemiology and Public Health in the University of Edinburgh, where he published a number of high-impact influential articles in the fields of cardiovascular, respiratory and diabetes epidemiology.

In 2016 he was awarded a Wellcome Intermediate Clinical Fellowship, as well as the Wellcome-Beit Prize, to study treatment effectiveness in people with multimorbidity (multiple chronic diseases). His project will use Bayesian approaches to combine clinical trial data with large administrative healthcare databases. This work will be undertaken within the Institute of Health and Wellbeing in the University of Glasgow and the Centre for Research Synthesis and Decision Analysis at the University of Bristol.

David also works for the NHS as an Honorary Consultant in Public Health Medicine, based at NHS National Services Scotland. Alongside the other consultant staff, his role is to provide clinical and epidemiological support and leadership as part of the Information Services Division (ISD) of the Public Health Intelligence group. ISD delivers the information service which supports health and social-care in Scotland.

Professor Kate O'Donnell

Professor Kate O'Donnell is Professor of Primary Care Research and Development (General Practice & Primary Care) at the University of Glasgow. She joined General Practice and Primary Care as a lecturer in 1996 after working as an immunologist and then as co-ordinator of the West of Scotland Health Services Research Network in the then Department of Public Health, University of Glasgow. She is involved in both research and postgraduate education, including supervision of PhD and MD students.



Her research focuses on the organisation and delivery of primary care services, particularly for marginalised populations, and the evaluation and routinisation of primary care policy into practice. She has a particular interest in the application of theory to research, especially Normalisation Process Theory and candidacy, and in the integration of mixed methods in community-based research.

A key area of work focuses on migrant health, in particular the role of language and communication in cross-cultural consultation in primary care and understanding the experience of asylum seekers, refugees and migrants when accessing and using primary care services. Other work has focused on primary prevention, in particular in relation to the development of dementia in later life and in the prevention of cardiovascular disease in socioeconomically deprived communities, on the use and implementation of digital health interventions and on the organisation of out-of-hours primary care.

Kate is a passionate advocate for academic primary care. She is the current Chair of the Society for Academic Primary Care (<https://sapc.ac.uk/>), where she champions the role of academic primary care and supports both clinical and non-clinical early career researchers. She is on the Advisory Board of the European Forum for Primary Care and a member of the NAPCRG International Committee. In recognition of this, Kate was recently awarded an Honorary Fellowship of the Royal College of General Practitioners, the highest honour the College can bestow on someone who is not a GP.

Professor Alan Silman FMedSci



Professor Alan Silman is Professor of Musculoskeletal Health at the University of Oxford. He is an epidemiologist and a rheumatologist. He was Director of the UK's Arthritis Research Epidemiology Unit at the University of Manchester between 1988 and 2006 and has published over 500 articles in the broad field of arthritis and musculoskeletal diseases. His research interests covered pharmaco-epidemiology, genetics and disease outcome; research that spanned several musculoskeletal disorders.

Professor Silman then became Arthritis Research UK's (ARUK) first Medical Director, a post he held from 2007 until the end of 2014. At ARUK he was responsible for the strategic direction of the charity's research activities as well as leading on both healthcare professional and patient education initiatives.

Currently he is Professor of Musculoskeletal Health at the University of Oxford. Amongst his other roles, he chairs appeal panels for NICE, advises the Medicines & Healthcare products Regulatory Agency (MHRA) on drug safety and is one of the editors of the leading international postgraduate textbook, *Rheumatology* (6th Edn. Elsevier 2014).

Dr Kathryn Skivington

Dr Kathryn Skivington is a Research Fellow at the MRC/CSO Social & Public Health Sciences Unit at the University of Glasgow. Kathryn graduated from the University of Aberdeen with an MA in Psychology (2004) and later went on to complete an MSc in Health Services Research and Public Health (2007). Kathryn joined the Unit's Evaluating the Health Effects of Social Interventions team in 2008 as a research assistant. She worked on an evaluation project looking at a government intervention aiming to support Incapacity Benefit claimants into employment.



She began studying for a PhD in 2009; the focus of the doctoral research was policy changes to Incapacity Benefit, related to the barriers to work that benefit recipients are confronted with, and the health impact of transitions in and out of employment. It involved quantitative and qualitative research in and around Glasgow.

After completing periods of employment at the Institute of Work and Health in Toronto and the Scottish Government in Edinburgh, Kathryn returned to the Unit in 2014 to work in the Neighbourhoods and Health programme. She is currently pursuing research to investigate the role of community links and social prescribing as a means of providing appropriate services to address health problems that are to some extent determined by socio-economic factors, such as unemployment.

Professor Graham Watt CBE FRSE FMedSci



Graham Watt was Norie Miller Professor of General Practice at the University of Glasgow from 1994 to 2016. He trained in general practice, public health and epidemiology and has carried out research in each area, including a series of studies on multimorbidity with Professor Stewart Mercer.

He has a long standing interest in health inequalities, especially the inverse care law. He coordinated General Practitioners at the Deep End from 2009 to 2016, working with GPs serving the 100 most deprived communities in Scotland. Similar projects have been established in Ireland, Yorkshire/Humber and Greater Manchester. In 2018 he was awarded the Saltire Society Fletcher of Saltoun Award for Science.

Engaging with industry

Professor Ed Bullmore FMedSci

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Professor Fiona Denison

Fiona Denison is a Professor of Translational Obstetrics at the University of Edinburgh and Honorary Consultant Obstetrician in NHS Lothian (Clinical Lead for Maternity Obesity Services). She is passionate about interdisciplinary research and believes that working across traditional research boundaries and challenging established fields of research is the only way to drive forward world-leading innovation across the life sciences sector.

She is currently leading the development of five novel medical devices with engineers, companies and clinicians and is Chief Executive Officer of a start-up company (Birthing Solutions Ltd) for one of these devices. She is Vice-Chair of the NICE Medical Technology Advisory Committee, has run multi-centre Health Technology Assessment funded clinical trials and is Chair of the External Steering Group for a Heriot Watt University Engineering and Physical Sciences Research Council Platform grant for medical device manufacture.



Dr Phil Murphy



Phil Murphy heads clinical imaging for GSK supporting imaging for experimental medicine studies through to standard endpoints for regulatory filing. Our group partners extensively with academic and industrial collaborators to identify new imaging technologies, develop methods towards clinical application and then deploy within clinical trials.

Phil has been applying clinical imaging in industry for over 15 years at Pfizer and GSK). Phil's academic background is in magnetic resonance with a Ph.D. from the Institute of Cancer Research, University of London in MR Spectroscopy of brain tumours.

Alex Papachronopoulos

Alex joined the University of Edinburgh in April 2016. His current role involves contract negotiations, development of effective working relationships with key decision makers in the biopharmaceutical industry and advice on funding routes and potential industry partners.

Previously he had worked in sales and business development roles for eight years in a company called MSD/VIANEX, the biggest Greek pharmaceutical company, responsible for promoting Merck's product in the Greek pharmaceutical market. Alex holds an MSc in Pharmaceutical Marketing and an MBA with distinction from the University of Strathclyde.



Professor Tariq Sethi

Professor Tariq Sethi is Chief Physician Scientist, Vice President AstraZeneca and Emeritus Professor of Respiratory Medicine Kings College London. He was previous head of the Respiratory Immunology Autoimmunity Translational Medicine Unit. Prior to joining AZ he was Head of Respiratory Medicine at Guy's, St. Thomas' and King's College Hospital NHS Foundation Trusts and Professor of Respiratory Medicine King's College London and formally Professor at the University of Edinburgh.



He was educated at Cambridge and London Universities followed by hospital jobs in London. He did a Ph.D at the Imperial Cancer Research Fund London, was an MRC Travelling Fellow at the Scripps Research Institute California and a Wellcome Trust Senior Research Leave Fellow in Edinburgh. His research interests focus on the interaction between inflammation and lung cancer.

Prof. Sethi continues on the editorial board of THORAX and was formally a member of the Population Systems Medicine Board Medical Research Council UK, Chair of Asthma (UK) and member of the British Lung Foundation Scientific Committees. He is also a Co-Founder of Galecto Biotech.

Dr Daniel Swerdlow



Dan works on building and deploying BenevolentAI's translational medicine and 'omics capabilities, seeking to derive greatest value from clinical and molecular data about large numbers of individuals for drug discovery using machine learning. He brings clinical insights to the design of workflows in these data and to the interpretation of their findings. He also leads on data stewardship at BenevolentAI, ensuring excellence in all data handling for drug discovery.

Prior to joining BenevolentAI, Dan worked in genomics-driven drug development at Genomics plc in Oxford. He was previously an academic clinical fellow in clinical pharmacology and therapeutics at Imperial College, having trained on the MBPhD programme at UCL, and continues to practice in acute medicine.

In his academic role at University College London, he has led a number of international research consortia using genetics for drug target identification and validation in cardiometabolic disease.

Competition abstracts

Post-Doctoral Plenary Competition

Dr Abhishek Das

Academic Clinical Lecturer in Infectious Diseases / Microbiology

London School of Hygiene and Tropical Medicine

Evaluation of a novel innate CXCL8+ effector T cell in neonatal bacterial infection

Background

Neonatal sepsis accounts for over one million annual deaths. Neonates classically have impaired T-helper 1 and 17 responses, contributing to sepsis vulnerability. We have identified CXCL8 as a novel effector capacity of neonatal CD4+ T cells (CXCL8 is a prototypic innate cytokine and potent neutrophil chemo-attractant). Herein, we determine function of T cell derived CXCL8 and correlation with sepsis severity and, in vitro, track their development into conventional adult adaptive subsets.

Methods

Fate: Using a novel method to isolate single cord-derived CD4+ T cells from an ELISPOT plate, we track the fate of clones derived from CXCL8+ T cells over time (flow cytometry for IFN-gamma/IL-4/IL-17a/transcription factors including T-bet).

Function: In a subset of pre-term neonates with inflammatory diseases (necrotising enterocolitis) or bacterial sepsis (E. Coli), we characterise T-cell CXCL8 production before and after sepsis, as a first look towards its potential function in vivo.

Findings

CXCL8+ T cell fate (thymus to periphery): We first demonstrated that CXCL8 is produced by thymocytes, prior to T cell receptor signalling. We next confirmed that CXCL8+ cells were analogous to the recent thymic emigrant population, through analysis of T cell receptor excision circles. Once egressed from the thymus, CXCL8+ T cells could then directly convert from an 'innate-like' cell to an adaptive T helper-1 cell. These data demonstrate a novel pathway of Th1 development.

In vivo, CXCL8+ T cells are detectable in situ within inflamed gut tissue in necrotising enterocolitis and peripheral frequencies peak with C-reactive protein in neonatal sepsis with E coli bacteraemia. CXCL8 production may therefore represent an early innate defence against bacterial infection.

Interpretation

Significance: We propose and highlight that neonatal T cell responses are not inert by default as once thought, rather CXCL8 production represents a robust, pro-inflammatory, though qualitatively distinct, feature of neonatal cells. Further data on this and other neonatal specific effector responses will provide candidate pathways which may be boosted to aid vaccine efficacy.

Strengths: In vivo data, determining CXCL8+ T cell enrichment in sepsis.

Limits: Preliminary observations in vivo.

Wider implications of your research

Neonatal T cell responses are often described as immature, tolerised or skewed towards a regulatory phenotype. We demonstrate that, in contrast, the first T cells exiting the thymus exhibit profound pro-inflammatory capacity through CXCL8 production. Furthermore, CXCL8+ T cells can transition from 'innate-like' effectors directly into adaptive IFN-gamma producers, describing a novel pathway of Th1 development.

These data unearth CXCL8 as a previously unrecognised qualitative function in neonates; such pathways may thus be amenable to manipulation for immune-therapy and optimisation of vaccine and adjuvant design. CXCL8 may also represent a candidate biomarker of inflammation in preterm infants with sepsis, in whom conventional markers including C-reactive protein are often insensitive.

Dr Annemarie Docherty

Clinical Lecturer

University of Edinburgh / NHS Lothian



Under-recognised, modifiable and causally-related to outcome: myocardial injury in critically ill patients with cardiovascular disease

Background

Critically ill patients with co-existing cardiovascular disease are at risk of myocardial infarction, however diagnosis is difficult in critical illness.

Objectives:

To establish the incidence of myocardial infarction in patients admitted to ICU with co-existing cardiovascular disease, and explore whether a causal relationship exists between acute physiological derangement, myocardial injury and infarction, and six-month mortality.

Methods

In a multicentre prospective cohort study in 11 UK ICUs we enrolled critically ill patients with co-existing cardiovascular disease. We measured troponin I (cTnI) with a high sensitivity assay for ten days, and ECGs for five days. cTnI data were concealed from clinicians; ECGs were interpreted by blinded cardiologists. Patients were categorized as 'infarction', 'injury' or 'no injury' according to the third universal definition of myocardial infarction. Patients were followed-up for six months.

Findings

cTnI was detected in all patients (n=273), demonstrating a rise/fall pattern consistent with acute injury. 73% of cTnI peaked on days 1-3 (median 114ng/l (1st,3rd quartiles; range: 27, 393; 3-58820). Serial ECGs indicated 24.2% (n=66) of patients experienced infarction and 46.1% (n=126) injury; only 30.8% (n=84) demonstrated no injury. Injury and infarction were significantly associated with six month mortality (reference: no injury): OR Injury 2.28 (95% CI 1.06-4.92, p=0.035), OR Infarction 2.70 (95% CI 1.11-6.55 p=0.028). cTnI partially mediated the relationship between acute physiological derangement and six month mortality (p=0.035) suggesting oxygen supply-demand imbalance as the likely mechanism of infarction (Type 2 MI).

Interpretation

Myocardial injury and infarction are common but rarely diagnosed in critically ill patients with co-existing CVD, and are associated with lower long-term survival. There was both a direct effect of acute physiological derangement on mortality (as expected), but importantly also a mediated effect by which it indirectly affected mortality through cTnI. This supports the findings that MI in this population is likely to be predominantly secondary to an oxygen supply-demand imbalance.

Wider implications of your research

I found that MI is likely to be predominantly secondary to an oxygen supply-demand imbalance (Type 2 MI). It follows that interventions aimed specifically at rectifying this imbalance may be beneficial for both MI but also plausibly for mortality. This is the first time, to my knowledge, that this has been demonstrated and has important potential clinical implications.

In contrast to broader literature, my systematic review, published in the BMJ, showed that a restrictive transfusion threshold less than 80g/l may not be safe in patients with co-existing CVD.

Both these pieces of work support my hypothesis that patients with co-existing CVD may benefit from increased oxygen delivery to the myocardium, and identify the need for an RCT of blood transfusion thresholds in this population.

Dr Muzaffer Kaser

NIHR Clinical Lecturer

University of Cambridge, Department of Psychiatry



Computational Approach to Reinforcement Learning in Patients with Remitted Depression: Results from a Randomised Double-Blind Placebo-Controlled Study

Background

Depression is associated with dysfunctional reinforcement learning, and blunted reward responsiveness can persist in patients with remitted depression. Persistent reinforcement learning deficits in depression can be a target for treatment. Modafinil was shown to improve performance in reward-based tasks. In this study, we investigated the effects of modafinil on reinforcement learning by using computational modelling that can provide a detailed account of the behavioural changes.

Methods

59 patients with remitted depression participated in this randomised, double-blind, placebo-controlled study that took part in Cambridge. The participants received single dose of 200 mg modafinil or placebo in parallel-groups and completed cognitive testing. We performed a detailed analysis of trial-by-trial behaviour using hierarchical models of reinforcement-learning that yielded learning rates and choice stochasticity (temperature) at the individual level.

Findings

The reinforcement learning data from 59 patients were analysed (Modafinil $n=29$, Placebo $n=30$). Modafinil led to an increase in choice stochasticity (temperature) in the punishment domain only, when compared to the placebo group ($F(1,57)=24.74$, $p<0.001$). Temperature-punishment is correlated with monetary gains ($r=-0.44$, $p=0.016$) and the attention performance ($r=-0.42$, $p=0.019$) in the modafinil group but not in the placebo group. This suggested that patients in the modafinil group were more in tune with the attentional processes and had higher monetary gains when making decisions following a punishment. There were no major side effects, and the other side effects (headache, insomnia) were not different between groups.

Interpretation

Modafinil seemed to work towards an increased exploration (i.e. searching for less punishing — or 'better' — opportunities) in punishment-based learning, and this effect was associated with more monetary gains and better attention performance. Modafinil's effects on striatal and prefrontal dopaminergic systems may have played a role. Computational approaches to reinforcement learning along with other cognitive test scores can help identify subtle behavioural differences within the samples.

Wider implications of your research

My research aims to understand the role of cognition in mood disorders and the underlying biological and behavioural mechanisms. In the wider context, my research will help emphasizing the cognitive dysfunction in depression as a public health problem. The impact of cognitive problems in work and social functioning is huge, and with a better understanding the link between mood disorders and cognition, the work environment and support mechanisms can be adjusted accordingly. Expansion in the use of cognitive testing via mobile devices can help new technological developments that will eventually guide re-organising the clinical practice and occupational settings.

Dr Kate Marks

ACF ST1 Histopathology

University of Leeds



An assessment of the mutation rate of normal colorectal epithelium in patients with cancer compared to patients without

Background

It is thought that half of somatic mutations present in colorectal cancers have arisen previously in the colorectal epithelium. In order to become fixed, these mutations must occur in colonic stem cells which can then replace the crypt. To study the mutation rate we used a neutral clonal marker, MAO-A. It is located on the X chromosome and truncating mutations result in loss of staining of the protein with immunohistochemistry allowing for direct visualisation of fixed mutations.

Methods

Normal colonic mucosa from examined from cancer patients (cancer-associated normal, CAN) N=10 and patients who had resections for non-neoplastic and non-inflammatory indications (non-neoplastic normal, NNN) N=7. Slides were stained for MAO-A and digitally scanned. We measured the total mucosa area and scored 300 random points as either epithelium, lamina propria or non-relevant. We then measured 50 randomly selected crypts per section to estimate the average crypt size and total crypt number.

Findings

For the 10 samples of CAN the average mutation rate was 1 in 2642 crypts. The 6 samples of NNN had an average mutation rate of 1 in 6737; this meant a 2.6 fold difference for CAN compared to NNN. The difference between the two groups was significant ($p=0.0198$). The average age of the patients in the two groups was similar; 72 for the CAN samples compared to 69 in the NNN group and this difference was not significant ($p<0.516$). There was an increase in the mutation rate seen with increasing age in both groups; the lowest mutation rate was 1 in 12,842 for a patient who was aged 44 compared to the highest rate of 1 in 901 crypts for an 88 year old patient. On average, the proportion of mucosa that contained epithelial tissue was 58% (range 42%-67%).

Interpretation

Mutations accumulate throughout the colorectal epithelium during a person's lifetime and are present in histologically normal mucosa before cancer occurs. By using a neutral clonal marker, MAO-A, we have shown a difference in the mutation rate of the normal mucosa from patients with cancer and without. Although a relatively low sample size, we have still demonstrated a clear significant difference of 2.6-fold. This may indicate more genetic damage occurring in the colorectum of cancer patients.

Wider implications of your research

The key to improving outcomes in colorectal cancer is by early detection and prevention. In order to prevent disease, one must first understand how it occurs. My research is around characterising the chances that occur in the normal colorectal mucosa before cancer develops. By understanding the dynamics of these changes we may be able to eventually exploit these to prevent cancer from developing. For my future work I hope to study how the difference in mutation rate of MAO-A in normal mucosa between cancer and non-cancer patients may reflect further genomic changes to fully characterise the amount of genetic damage in normal mucosa. Also I would like to investigate how levels of genetic damage may relate to the microbiome which could be the underlying driver behind these changes.

Pre-Doctoral Plenary Competition

Dr Duncan Brian

CRUK Clinical Research Fellow

University College London



Forced expression of retinoic acid receptor alpha potentiates differentiation of acute myeloid leukaemia

Background

Cytotoxic chemotherapy forms the backbone of AML treatment, save for promyelocytic leukaemia (comprising 10% of AMLs). This subtype is uniquely sensitive to retinoic acid + arsenic, due to it being driven by a retinoic acid receptor alpha (RARA) containing fusion protein. In normal haematopoietic stem cells retinoid signalling is able to induce myeloid differentiation. We sought here to discover whether non-promyelocytic AMLs could be forced to differentiate by manipulation of RARA signalling.

Methods

AML cell lines (HL60, MUTZ-3 and NB4) were obtained from DSMZ or ATCC. Lentiviral forced expression vectors driven by an SFFV promoter expressing retinoic acid receptor and GFP were generated in-house. Cells were treated with vectors expressing RARA or control, followed by retinoid treatment 48 hours later. Myeloid differentiation was assayed on day 7 by immunophenotyping and morphological assessment. Forced expression was confirmed by western blotting and qPCR.

Findings

We show here that forced expression of retinoic acid receptor alpha using a lentiviral expression system allows potentiation of terminal differentiation in non-promyelocytic leukaemias in response to retinoid therapy. For HL60 cells, GFP+CD11b+ positive cell fractions increased from a mean of 0.1% to 4% in response to retinoid treatment in control vector-treated cells but from 0.2% to 51% for retinoid treated cells subject to RARA forced expression. In MUTZ-3 cells the mean fraction of GFP+11b+ cells increased from 3% to 30% after retinoid treatment in control vector-treated cells and compared to 0.7% to 95% after retinoid treatment in the context of forced expression of RARA. Changes in morphological appearances were consistent with the differentiated immunophenotype.

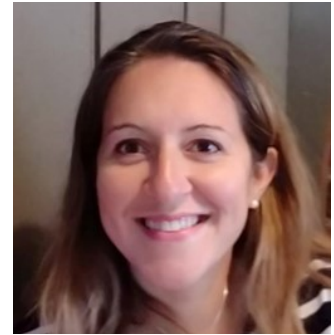
Interpretation

Targeting transcriptional networks that control terminal differentiation represents a potential route to developing novel therapies for AML. Here we demonstrate the potential for differentiation responses to retinoic acid in the context of increased retinoid receptor expression. Identification of drugs that upregulate receptor expression or cellular retinoid responsiveness may therefore represent a useful avenue to enabling retinoid therapy in other acute myeloid leukaemia subtypes.

Dr Tessa Cacciottolo

Wellcome Trust Clinical Research Fellow

WT-MRC Institute of Metabolic Science, University of Cambridge



Rare Variants in Steroid Receptor Coactivator 1 (SRC-1) associated with Severe Obesity

Background

Whilst the rising prevalence of obesity is largely driven by changes in the environment, genetic factors play an important role in weight regulation. Rare variants in genes encoding leptin and its targets in the hypothalamus (including pro-opiomelanocortin (POMC)) are associated with severe obesity, demonstrating the pivotal role of this pathway. The aim of this study was to explore the mechanisms that may explain the obesity seen in mice lacking Steroid Receptor Coactivator-1 (SRC-1).

Methods

We characterised mice with targeted deletion of SRC-1 in Pomc neurons and used invitro assays to explore the molecular mechanisms by which SRC-1 modulates Pomc expression. In humans, we interrogated exome sequencing and targeted resequencing data on 2548 individuals with severe obesity and 1117 non-obese controls. We also characterised the phenotype of SRC-1 variant carriers by measuring body composition, energy intake at an ad libitum test meal and energy expenditure using indirect calorimetry.

Findings

In cells, we found that leptin-induced phosphorylated STAT3 interacts with SRC-1 to modulate Pomc expression. Mice with a targeted deletion of SRC-1 in Pomc neurons showed increased food intake and weight gain on a high fat diet, demonstrating the physiological relevance of this mechanism. Fifteen rare heterozygous variants in SRC-1 were found in obese people; these resulted in a loss of function in cells studied using a POMC reporter assay, whilst 4 variants found in non-obese controls were comparable to wild-type SRC-1. Variant carriers exhibited increased ad libitum energy intake, whilst basal metabolic rate was comparable to that predicted by body composition. A knock-in mouse model of a human loss of function variant, L1376P, also exhibited increased food intake and weight gain.

Interpretation

Disruption of SRC-1 causes obesity in mice and is likely to contribute to severe obesity in humans. This study showed that one potential underlying mechanism is that SRC-1 interacts with phosphorylated STAT3 to modulate Pomc expression and thus the acute appetite suppressing effects of leptin. These findings pave the way for clinical trials of a melanocortin 4 receptor agonist (the downstream target of POMC) in SRC-1 variant carriers.

Dr Judith Harrison

Wellcome Trust GW4 Clinical Academic Fellow

Cardiff University

Identifying biological pathways to Alzheimer's Disease using MRI markers and polygenic scores: a cross-sectional study

Background

Single nucleotide polymorphisms (SNPs) contribute small increases in risk for late-onset Alzheimer's Disease (LOAD). LOAD SNPs cluster around genes with similar biological functions (pathways). Polygenic risk scores (PRS) aggregate the effect of SNPs genome-wide. Polygenic risk for LOAD is associated with decreased brain volumes in key regions. This approach has not been used for SNPs within specific pathways. We investigated whether pathway-specific PRS were associated with brain volumes.

Methods

Our discovery sample was the International Genomics of Alzheimer's Project (25,580 cases, 48,466 controls). We mapped SNPs to genes in 8 pathways implicated in LOAD. The risk allele threshold was $p = 0.5$. The target sample ($N = 670$, aged ~24) were from the Avon Longitudinal Study of Parents and Children. Genetic data were pruned with $r^2 < 0.2$. Cortical thickness and subcortical volumes were calculated using FreeSurfer. We used linear regression, adjusting for sex and intracranial volume.

Findings

We ran 360 tests (8 polygenic scores \times 45 MRI measures). P values were corrected using the false discovery rate. Polygenic scores were significantly associated with changes in cortical thickness and sub-cortical volume. For example, the immune response pathway was associated with lower cortical thickness in 7 regions: the left rostral anterior cingulate ($p = 0.002$, $r^2 = 0.035$); the posterior cingulate, right ($p = 0.014$, $r^2 = 0.011$) and left ($p = 0.039$, $r^2 = 0.008$); the right lateral orbitofrontal ($p = 0.019$, $r^2 = 0.018$); the right caudal middle frontal ($p = 0.026$, $r^2 = 0.021$), the left insula ($p = 0.047$, $r^2 = 0.009$) and the right precentral cortex ($p = 0.047$, $r = 0.017$). It was associated with increased cortical thickness in the right pericalcarine area ($p = 0.043$, $r^2 = 0.014$).

Interpretation

LOAD disease pathway-specific polygenic risk was associated with decreased cortical thickness in a number of brain regions in healthy young adults. Thus, genetic risk for LOAD pathways can be linked to structural differences in the brain many decades before potential illness onset. Strengths of this study include our large discovery sample size. Future analyses will explore the contribution of APOE to the polygenic risk score and will include larger target sample sizes.

Dr Jonathan Hazlehurst

Academic Clinical Lecturer

University of Birmingham

Obstructive sleep apnoea is associated with activation of the hypothalamic pituitary adrenal axis but antagonism of the glucocorticoid receptor is unlikely to prevent the associated metabolic disease

Background

Obstructive sleep apnoea (OSA) and states of glucocorticoid (GC) excess are both associated with a significant burden of metabolic disease. Whether GCs are elevated in OSA and contribute to this metabolic dysfunction is unclear. Aims: 1) To determine if GCs are elevated in patients with OSA using a CPAP (continuous positive airway pressure) withdrawal model. 2) To determine whether antagonism of GCs may be metabolically beneficial in a human experimental model of intermittent hypoxia.

Methods

1:23 patients with OSA on CPAP were randomised to either continued (n=11) or sham CPAP (n=12) for 2 weeks. Patients provided a urine sample for steroid GCMS pre and post intervention (REC12/SW/0254). 2:17 healthy volunteers underwent a detailed assessment of carbohydrate and lipid metabolism in air and then again after 1 week of either no treatment (n=9) or the GC antagonist RU486 (n=8) in conditions of acute intermittent hypoxia (10 desaturations/hour to 85-91% oxygen for 6 hours) (REC15/EM/0308)

Findings

Sham CPAP for 2 weeks was associated with a return of OSA (oxygen desaturation index increased (5.3±4.9 to 49.6±26.2 vs continued CPAP 7.1±6.5 to 6.5±4.8; p<0.001). GC specific urine metabolites increased in the sham CPAP group (Total GC: 3664.2±1456.9 to 4040.1±1104.7; continued CPAP 3206.4±1824.8 to 3108.6±1117.0 µg/12 hours; p=0.03).

The acute intermittent hypoxia (AIH) model successfully replicated desaturation pattern of OSA (11.4±0.8 desaturation/hr, 87±4 %O₂ saturations). AIH had no effect on global glucose metabolism or adipose tissue metabolism. AIH was associated with increased hepatic de novo lipogenesis (1.69±0.7 to 2.54±1.4 VLDL% DNL.hr; p=0.04) as well as increased hepatic insulin resistance. GC antagonism was not metabolically protective from AIH and was associated with rash.

Interpretation

Nocturnal urine collection for GCMS offers the most robust assessment of GC secretion to date in OSA and showed that treatment with withdrawal increased GC secretion. This may contribute to metabolic disease in OSA. The AIH model may have been too acute to see changes in glucose metabolism and was limited by small numbers. However, given the failure of GC antagonism to show benefit and the association in some with a self-limiting rash it does not support extending this study to patients with OSA.

Dr Gareth Kitchen

MRC Clinical Research Training Fellow

University of Manchester

Circadian regulation of macrophage phagocytosis is mediated by a REV-ERBa independent BMAL1/RhoA pathway

Background

Bacterial infections are differentially affected by time of day, but the mechanisms underlying this effect remains undefined. Our previous work has identified a BMAL1:REVERB circuit as an important negative regulator of acute, neutrophilic inflammation, but the role of this circuit in macrophage phagocytosis has not been determined. Therefore, we initially deleted BMAL1, and in subsequent studies REVERB in macrophages and examined responses to infection in-vivo, and in ex-vivo culture.

Methods

A mouse model of pneumococcal pneumonia carried out in murine driver lines targeting conditional deletion of BMAL1 in macrophages. Bacterial burden was assessed in lung and blood. In vivo and ex vivo phagocytosis assays with *S. Aureus* - pHrodo green fluorophore enabled FACS and microscopic assessment of phagocytosis. Actin microscopy, RhoA activation assays and phosphoproteomic analysis characterized activation in BMAL1 deleted macrophages.

Findings

LysMxBMAL1 and CX3CR1xBMAL1 murine strains had lower bacterial burden to airway pneumococcal infection, identifying macrophage clock control of infection. This was not observed in LysMxREVERB α DBDm or light disrupted mice. In vivo studies showed LysMxBMAL1f/f mice had increased phagocytosis following intraperitoneal injected labeled bacteria. Ex vivo peritoneal macrophages exhibited increased phagocytosis in the absence of Bmal1, whereas neutrophils did not. REVERB α DBDm KO macrophages showed no phagocytic phenotype. BMAL1 $^{-/-}$ macrophages showed actin cytoskeleton differences, reduced p-cofilin and RhoA activation. Phagocytosis assays in the presence of a RhoA inhibitor normalized phagocytosis in BMAL1 $^{-/-}$ macrophages to the level of control mice.

Interpretation

We show a surprising gain of anti-bacterial function through loss of BMAL1 in macrophages. REVERB α , previously found to be an essential link in clock control of inflammation, is not involved in macrophage phagocytosis. RhoA is identified as a BMAL1 target in macrophages, and is thus an essential link between BMAL1 and macrophage phagocytosis.

Dr Angela Lucas-Herald

Clinical Research Fellow

University of Glasgow

Altered vascular function in boys with hypospadias- role of reactive oxygen species

Background

Hypospadias in boys may be associated with a lack of androgen exposure during the masculinisation programming window. As testosterone has effects on the vasculature, we assessed whether boys with hypospadias show any evidence of vascular dysfunction.

Methods

Excess foreskin tissue was obtained from boys undergoing hypospadias repair (cases) or circumcision (controls) and small arteries dissected from this tissue. Vascular contractility was assessed by wire myography in response to U46619 (thromboxane A2 analogue). Vascular smooth muscle cells (VSMCs) were cultured and generation of reactive oxygen species (ROS) was measured by amplex red and chemiluminescence. NADPH oxidase (Nox) mRNA expression was measured by qPCR.

Findings

19 cases and 22 age-matched controls were enrolled in this study (median age 1.9 (range 1.3, 12.2) years). Arteries from cases demonstrated increased constriction to U46619 compared to controls (Emax: 175.6 vs 66.3 $p < 0.001$), an effect inhibited by the ROS scavenger N-acetylcysteine (NAC). VSMC superoxide anion (5.3 fold) production and H2O2 (3.3 fold) levels were increased in cases compared to controls ($p < 0.05$). Expression of Nox5, a major ROS-generating oxidase in vascular cells, was increased in cases (2.6 fold, $p < 0.05$). Exposure of vessels to testosterone increased vasoconstriction to U46619 (Emax: 66.3 to 124.6 $p < 0.001$) in controls, but not in cases. Incubation with NAC abolished the testosterone-induced vascular effects.

Interpretation

These novel data, from a unique cohort of patients, demonstrate that small arteries from boys with hypospadias exhibit increased vascular contractility and decreased vasorelaxation with associated increased Nox-derived ROS generation. The functional significance of vascular dysfunction in these boys is unclear, but may play a role in immediate surgical outcome as well as altered long-term cardiovascular risk.

Dr Carl Marincowitz

NIHR Doctoral Research Fellow

Hull York Medical School



The impact of the SIGN head injury guidelines and NHS 4-hour Emergency Target on hospital admissions for head injury in Scotland: An Interrupted Times Series

Background

There are over 1.4 million annual attendances to Emergency Departments in the UK following head trauma. 1% of patients have life-threatening injuries, whilst most are discharged. National guidelines (SIGN) were introduced in Scotland with the aim of achieving early identification of acute intracranial lesions yet safely reducing hospital admissions. This study assesses the impact of these guidelines and any effect the 4-hour ED performance target had on hospital admissions for head injury.

Methods

An interrupted time series analysis for the period 1998 to 2016 was completed using monthly Information Services Division admissions data for all hospitals in Scotland. A time dependent model for the monthly rate of hospital admissions for head injury was estimated. A change in the level or trend in the model was assessed for at intervention points for each guideline (2000 and 2009) and the introduction of the 4-hour target (2004). Seasonality and autocorrelation were adjusted for.

Findings

Both guidelines were associated with a monthly decreasing trend in total hospital admissions per 100 000 population (Guideline 1:-0.14 (95% CI: -0.27 to -0.01); Guideline 2:-0.09 (95% CI:-0.13 to -0.05)). The introduction of the 4-hour target was associated with increased hospital admissions (0.13 (95% CI: 0.06 to 0.20)). In age groups with more indications for CT imaging within 8 hours of hospital attendance, the 4-hour target was associated with a larger increase in hospital admissions. Although the guidelines acted overall to reduce hospital admissions for head injury, both guidelines were associated with increased admissions for patients with brain injuries identified by CT imaging.

Interpretation

This is the first study to assess the impact of the SIGN guidelines and 4-hour Emergency Department target on hospital admissions for head injury. Increased CT imaging of head-injured patients recommended by SIGN guidelines reduced admissions indicating this may be a cost-effective strategy for the management of head injury. This effect was offset by an increase in the diagnosis of TBI. The 4-hour ED target appears to have undermined the guidelines' intended reduction in hospital admissions.

Dr Sarah Murray

Wellcome Trust Clinical Research Fellow, ST5 Obstetrics and Gynaecology

University of Edinburgh

Gestational age at delivery of twins and the risk of perinatal death: a Scottish population based cohort study

Background

Twin pregnancy is associated with a threefold increase in perinatal mortality compared to singleton pregnancies. Reduction of stillbirth and neonatal mortality is a major priority for the NHS in England/Wales and Scotland and optimizing the timing of delivery of twins is a key strategy in reducing these rates. The aim of this study is to determine the week of gestation associated with the lowest risk of perinatal death in twin infants to inform clinicians regarding timing of delivery.

Methods

A population based cohort study was performed with all twin pregnancies delivered at 34 weeks' gestation or greater from 1980-2015 in Scotland using routinely collected data. The primary outcome was perinatal mortality. To determine the association between gestation and perinatal death compared to ongoing pregnancies univariate and multivariate random effects modelling was performed. The study was approved by the National Health Services Scotland Privacy Advisory Committee.

Findings

The study population comprised of 43 4436 twin infants with a total of 472 stillbirths and infant deaths. 303 infants were excluded due to unreliable gestational age measurement, congenital anomalies and obvious data outliers leaving a cohort of 43 133 twin infants for analysis. Twin infants born at 34 weeks had an increased risk of perinatal death compared to ongoing pregnancies (adjusted odds ratio [OR], 3.27, 95% CI 2.34 - 4.57) as did delivery at 35 and 36 weeks (adjusted OR 2.06, 95% CI 1.49-2.84 and adjusted OR 1.34, 95% CI 1.01- 1.80 respectively). Delivery at 37 and 38 weeks were associated with the lowest risk of perinatal death compared to ongoing pregnancies (adjusted OR 0.52, 95% CI 0.37 - 0.71 and adjusted OR 0.50, 95% CI 0.36 - 0.69 respectively).

Interpretation

Gestation at delivery has a strong relationship with perinatal death with the lowest risk of death at 37 - 38 weeks' gestation compared to ongoing twin pregnancies. This information could be used when counselling women regarding timing of delivery of twin pregnancies. The main strength of the study lies in the sample size as to our knowledge this is the largest UK cohort study of twins. Limitations of observational studies like this include the risk of selection bias and residual confounding.

Poster Competition - Group A

A1 Dr Pete Dayananda
Specialty Trainee
University of Leeds

The potential utility of surveillance for carbapenemase resistant enterobacteriaceae (CRE) in hospital wastewater in a low CRE prevalence tertiary hospital setting

The spread of carbapenem resistant enterobacteriaceae (CRE) is a concern, as carbapenems are often a last resort antibiotic. CRE screening is based on collecting rectal swabs from patients with increased CRE colonisation risk. In low prevalence settings, this provides limited information. Hospital sewage harbours CRE and was explored as an indirect marker of CRE in a high CRE prevalence hospital. We piloted CRE quantification in hospital sewage in a low CRE prevalence tertiary hospital setting.

The study was conducted at Leeds General Infirmary. Clean and wastewater samples were collected to screen for CRE presence using chromID@CARBA agar. Wastewater samples (500x3mls) were collected from hospital sewage pipes corresponding to 5 wards between Aug-Sept 2017. Clean water samples (500x3mls) were collected from the same wards and day. Presumptive CRE isolates were identified using mass spectrometry. Isolates were tested for resistance to meropenem and ertapenem as per EUCAST criteria.

Carbapenem-resistant bacteria were isolated from 13/15 wastewater samples. Pseudomonas spp were isolated from all 13 samples. Suspected CRE isolates were recovered from 9/15 wastewater samples. Using MALDI-TOF MS, Aeromonas hydrophilia was identified in all 9 suspected samples and Klebsiella oxytoca was identified in 1 sample. Carbapenem-resistant K. oxytoca was isolated from 1/3 wastewater samples from paediatric haematology. Carbapenem-resistant bacteria account for 6.66% of bacteria in wastewater and were not isolated from clean water.

Carbapenem resistant Pseudomonas spp. is readily isolated from wastewater samples. The single CRE isolate (K. oxytoca) was from a paediatric haematology ward from which no recent (27 months) CRE patients were identified. Targeted sampling of wastewater from areas with high antimicrobial consumption, such as oncology, may be a useful way of detecting missed CRE colonisation, and act as an early-warning of increasing prevalence of these key pathogens in (perceived) low-CRE prevalence settings.

A2 Dr Alison Gifford
Paediatric Specialty Trainee
University of Dundee

Worldwide short course education programmes in epilepsy for paediatricians - are they effective? An international survey.

The UN Sustainable Development Goals include reduction in premature mortality from non-communicable disease and training of the healthcare workforce. Peer-supported workshop-based training is a proven effective training tool. The PET (Paediatric Epilepsy Training) programmes have recently expanded across five continents. A one day standardised curriculum promotes evidence-based, safe practice which is delivered by a trained faculty to a target audience, primarily paediatricians.

A pragmatic framework was used to measure the effectiveness of these courses following the Kirkpatrick framework of course outcome evaluation. Data was recorded on attendance, reaction to the course delivery by immediate feedback forms on satisfaction and knowledge gain by pre- and post-course quiz. A 'Changes in Attitudes and Practice Survey' was sent to participants from India, Kenya, Myanmar, New Zealand, South Africa, Sudan and the UK six months following the course.

6781 clinicians attended a PET Level 1 course over the last 15 years. Level of seniority and experience did not affect participants' positive reaction ($R^2 = 0.05$). Knowledge scores pre and post course increased from 76% to 90%. 323 participants responded to the change in practice survey. 66% reported significant or moderate changes to their personal practice in epilepsy care. In 2017, specific improvements included improved history-taking (82%), ability to distinguish epileptic and non-epileptic events (85%), no longer prescribing anti-epileptic drugs for febrile seizures (42%) and improved prolonged seizure management (54%). A clear trend to greater reported improvements from low and middle-income country settings was seen.

Outcome evaluation not only aids the development of course content and format, but acts as evidence that limited resources are being used effectively. This data provides evidence for the effectiveness of short-course epilepsy education for clinicians to improve the quality of care for children with epilepsy globally.

A3**Dr Sophie Gu**Academic Clinical Fellow in Cardiology
Newcastle University**Recurrent myocardial infarction is an independent predictor of cognitive decline in older patients with non-ST elevation acute coronary syndrome: a prospective cohort study**

Dementia is a growing health burden of an ageing population. There are no previous studies evaluating cognitive impairment in older patients with non-ST-elevation acute coronary syndrome (NSTEMACS) undergoing invasive care in the setting of an ageing population. This study aims to evaluate the prevalence of cognitive impairment (CI) and the predictors of cognitive decline at 1 year in this high-risk older NSTEMACS patient group.

Patients with NSTEMACS, aged ≥ 65 years and referred for urgent coronary angiography \pm percutaneous coronary intervention (PCI), were recruited. Cognitive assessment was examined using the Montreal Cognitive Assessment (MoCA) score. The composite major adverse cardiovascular events (MACE) comprised death, myocardial infarction (MI), unplanned revascularisation, stroke and significant bleeding at 1-year.

Of 271 patients who had cognitive assessment at baseline, 211 had MoCA at 1 year. Median follow-up was 366 days (interquartile range 10). The mean age of participants was 80.4 ± 4.8 years; 170 (62.3%) were male. There was a high prevalence (48%) of cognitive impairment at baseline. Patients with CI experienced higher MACE rates at 1-year (30.2% vs. 19.9%, $P=0.049$) compared to normal patients. There is a significant reduction in MoCA score from baseline to 1-year (mean reduction 0.6 ± 3.3 , $p=0.007$). Seventy-four (35.1%) patients experienced cognitive decline (MoCA drop by ≥ 2 points) at 1-year. Decliners were more likely to be frail. Recurrent MI was an independent predictor of cognitive decline at 1-year (Odds Ratio [OR] 3.34, 95% CI 1.22-9.15, $p=0.02$) after adjustment of age and sex.

In older patients undergoing invasive management of non-ST-elevation ACS, there is a high prevalence of cognitive impairment at baseline. Recurrent myocardial infarction is independently associated with cognitive decline at 1-year. The actual mechanisms responsible for cognitive decline in this patient cohort are not clear. Early intervention and risk factor modifications are crucial in preventing cognitive decline.

A4**Mr Simon Haworth**Welcome Trust Clinical Research Training Fellow
University of Bristol**Apparent structure in the genetic data of UK Biobank creates biased causal estimates: a descriptive genetic epidemiology study**

The UK Biobank is an exceptional resource for understanding the aetiology of a broad range of diseases. Increasingly, researchers are using genetic variation to attempt to characterize the nature of relationships between traits, for example untangling causal from confounded relationships. Inference drawn from these analyses is contingent on the number and properties of genotypes used in them and it is unclear whether structure in (now large-scale) genetic data is present or might bias estimates.

Using UK Biobank data, genome-wide association studies were undertaken for birth location. Exemplar polygenic scores were derived and then regional differences in these scores were assessed using generalized additive models incorporating spline terms for birth location. Separately, the magnitude of bias in estimated relationships between polygenic scores and complex traits was explored by measuring the attenuation in these relationships when adjusting for geographical terms.

Analyses included up to 321,439 adult participants of British ancestry. Both individual genetic variants and polygenic scores showed evidence for association with location, which was attenuated but not completely removed by adjustment for study centre and 40 genetic principal components. This apparent structure is a source of covariance between genotypes and health outcomes which could be unrelated to biologically causal pathways. Analysis of real complex traits showed that the relationship between polygenic scores and complex traits could therefore be substantially overestimated, while analysis of simulated data showed this stratification can induce artefactual relationships indistinguishable from causal relationships.

The existence of apparent latent structure within the genetic data of UK Biobank is unsurprising, but important. This observation challenges naive interpretation of epidemiological analyses which use collections of genetic variants as proxy measures for exposures or health outcomes. Conversely, latent structure provides unexpected opportunities, for example regional genetic differences across the UK could be exploited to shed new light on the origins of regional inequalities in health.

A5 **Dr Geoffrey Martin**
Clinical Research Fellow in Pleural Disease
University of Glasgow and Queen Elizabeth University Hospital, Glasgow

Pre-EDIT: A randomised, feasibility trial of Elastance-Directed Intra-pleural catheter or Talc Pleurodesis (EDIT) in the management of Malignant Pleural Effusion

Non-expansile lung (NEL) is a common cause of talc pleurodesis (TP) failure in Malignant Pleural Effusion (MPE). NEL is frequently occult prior to drainage and more effectively managed using an indwelling pleural catheter (IPC). Elevated Pleural Elastance (PEL) is associated with NEL and may inform MPE management but evidence of patient benefit attributable to its measurement is lacking. Pre-EDIT is a randomised feasibility trial of Elastance-Directed IPC or TP (EDIT) management of MPE.

Eligible patients (symptomatic MPE, written informed consent and no prior evidence of NEL or IPC preference) are randomised 1:1 between EDIT (PEL assessment followed by TP or IPC insertion) and standard care (TP). The primary objective is to determine whether it is feasible to randomise 30 patients within 12 months (or 15 within 6 months). Pre-EDIT was approved by the West of Scotland Regional Ethics Committee (17/WS/0042) and is a registered clinical trial (clinicaltrials.gov NCT03319186).

23/30 patients have been recruited since opening on 28/8/17 (at time of submission). Fifteen patients were recruited during 6 months between October 2017 and April 2018. Preliminary results relating to secondary objectives (including assessment of the safety of EDIT management, the aspiration volume required to detect abnormal PEL and the frequency with which pneumothorax induction is required for subsequent TP/IPC) will be available in November 2018.

Pre-EDIT will prospectively address important areas of uncertainty regarding the design of a potential future Phase III trial of EDIT management using patient-centered outcome measures. Recruitment has reached a pre-specified feasibility threshold.

A6 **Dr Alexander Mehta**
Foundation Doctor Year 1
Royal Victoria Infirmary, Newcastle

Where to Draw the Line in Surgical Obesity for Renal Transplant Recipients: An Outcome Analysis Based on Body Mass Index

Renal transplant is the criterion standard treatment for patients with end-stage renal disease. Because obesity rates are increasing in the global population, international standards on renal transplant in obese patients remain a grey area. The aim of this study was to determine whether renal transplant remains the treatment of choice in an obese patient with end-stage renal disease.

We performed a retrospective analysis on all patients who underwent renal transplant in our transplant unit between 2008 and 2013. Patients were divided into 3 cohorts based on body mass index (cohort A was < 25 kg/m², cohort B was 25-29.99 kg/m², cohort C was ≥ 30 kg/m²). Postoperative complications within 90 days after transplant were assessed using one-way analysis of variance and chi-square distribution. Patient and graft survival rates over 3 years were assessed with Kaplan-Meier analyses

Of 610 total patients, 92 patients (15%) were classified as "obese" (≥ 30 kg/m²) in cohort C, with 294 patients in cohort A and 224 patients in cohort B (24 patients were excluded). Regarding short-term complications during the 90-day post-transplant period, obese individuals were at increased risk of a higher number of complications ($P = .039$ for cohort A vs cohort C). Lymphocele in particular was associated with obesity ($P = .004$); fortunately, this condition had no direct impact on the graft itself and was relatively easy to monitor and treat. The long-term outlook (3 years) appeared positive, with both graft survival (92% in cohort A, 91% in cohort B, and 94% in cohort C) and patient survival (97% in cohort A, 99% in cohort B, and 97% in cohort C) being independent of patient obesity.

Increased body mass index up to 37.5 kg/m² was not associated with increased risk of serious postoperative morbidity or mortality after renal transplant. Surgery should be considered as the criterion standard treatment for obese patients with end-stage renal disease if they are otherwise medically fit with few or well-controlled comorbidities.

A7

Dr Eve Miller-Hodges
ECAT Clinical Lecturer
University of Edinburgh

A change of heart: linking cardiovascular trials with routinely collected health data to assess cardiovascular risk in patients with kidney disease.

Cardiovascular disease (CVD) is the most common outcome of chronic kidney disease (CKD). The optimal strategies to diagnose, risk stratify and treat CVD in patients with CKD remain uncertain. Patients with CKD are often excluded or undifferentiated in clinical trials. We linked data from cardiovascular trials with routinely collected health data to clarify the role of high-sensitivity Troponin I (hs-TnI) and CT coronary angiography (CTCA) in the management of CVD in patients with CKD.

In 4726 patients with suspected acute coronary syndrome (ACS) we evaluated the performance of hs-cTnI in patients with and without renal impairment (estimated glomerular filtration rate <60mL/min/1.73m²) to diagnose and exclude myocardial infarction (MI). Subsequent MI and cardiac death were reported at one year. In an open label randomised clinical trial (SCOT-HEART) we determined the effect of renal function on the use of CT coronary angiography (CTCA) in 1314 patients with suspected angina. Renal impairment was common in unselected patients with suspected ACS (19%). Low hs-TnI levels (<5ng/L) identified patients at low risk of cardiac events, even with renal impairment (NPV 98.4%, 95%CI 96.0-99.7% vs. NPV 99.7%, 95%CI 99.4-99.9% for those without). The PPV and specificity for diagnosis of MI were lower in patients with renal impairment. At one year, 24% of patients with renal impairment and hs-TnI >99th centile had experienced further MI or cardiac death vs. 10% without.

Renal impairment was rare in the SCOT-HEART trial (4%). The effect of declining eGFR on survival from subsequent MI or cardiac death was ameliorated by the use of CTCA (adjusted HR 1.18; 95%CI 0.83-1.53 per fall of 10ml/min/1.73m² eGFR) as opposed to standard care (adjusted HR 1.42; 95%CI 1.16-1.47).

Linking trial data with routinely collected health data allowed specific analysis of the sub-group of high-risk patients with renal impairment. In suspected ACS, hs-cTnI stratified risk in patients with renal impairment in the short and medium term, identifying those patients who should be considered for further investigation and treatment. In suspected angina, CTCA appeared to be of particular benefit to patients with renal impairment.

A8

Dr Jasper Mogg
Academic Foundation Doctor
Newcastle University

Assessing strengths and weaknesses in online patient information in transplantation

The Internet is increasingly used as a source of information by transplant recipients and donors. However, the quality of the information that is accessed has not been formally assessed.

An iterative search strategy using Google Trends was used to identify unique search terms relating to each solid organ transplant. These terms were entered into Google, Yahoo!, and Bing, and URLs on the first pages collected. Four individuals reviewed each URL independently, using a customised DISCERN tool to assess the quality of information and to stratify the information as 'poor' (serious or extensive shortcomings), 'moderate' (potentially important but not serious shortcomings), or 'good'.

1,654 unique URLs were identified from 366 search terms. 393 URLs met inclusion criteria, covering 90% of all website traffic globally. 14% of webpages were assessed overall as good, 46% moderate, and 40% as poor. There was no strong correlation between page popularity and quality. Analysis of the 16 DISCERN domains revealed the best performance in: providing other sources of information, and information relevance. Domains with moderate performance included: describing risks and benefits of transplantation. Finally, the poorest performance was in: the effect of transplantation on quality of life, and support for shared decision-making.

Deficits in online patient information are likely to negatively affect informed consent in organ donation. Therefore, healthcare practitioners should focus on providing extra information in those domains identified as weak. Particular attention should be paid to: shared decision-making, risks and benefits of transplantation, and the effect transplantation has on the quality of life of the recipient.

A9 Dr Christoph Mueller
Academic Clinical Lecturer
King's College London

Antipsychotic use in dementia: The relationship between neuropsychiatric symptom profiles and adverse outcomes

Antipsychotics are known to carry a risk of major adverse health impacts in people with dementia. The authors aimed to explore whether risk of adverse outcomes related to antipsychotic prescribing in dementia differed in subgroups of dementia patients clinically classified as suffering from problematic psychosis, agitation or a combination.

A cohort of 12,980 patients with an outpatient diagnosis of dementia was assembled from a large dementia care database in South East London. Neuropsychiatric symptoms present at dementia diagnosis were determined according to Health of the Nation Outcome Scales (HoNOS65+) mental and behavioural problem scores and the sample was divided into four groups: 'agitated psychosis', 'agitation, but no psychosis', 'psychosis, but no agitation', and 'neither psychosis, nor agitation'.

Cox regression models were used to explore associations of antipsychotic prescription with survival, hospitalization and stroke. In the group 'psychosis, but no agitation', in which 41% were prescribed an antipsychotic, a significantly increased risk of mortality (Hazard ratio (HR) 1.31; 95% confidence interval (CI) 1.08-1.57) and stroke (HR 1.89; 95% CI 1.09-3.28) was detected in relation to antipsychotic prescribing after adjusting for a wide range of potential confounders. In patients with 'agitation, but no psychosis' a marginally increased risk of mortality emerged (HR 1.14; 95% 1.00-1.30). In patients with 'agitation & psychosis', no increased risk of mortality or stroke was detected.

The effects of antipsychotics in dementia are complex. Risks may be highest in those presenting with psychosis without agitation, indicating the need for novel interventions for this group. Clarification of risk profiles can inform a precision medicine approach to management of the most distressing feature of dementia.

A10 Dr Kelechi Njoku
NIHR ACF ST3
University of Leeds

Radiotherapy for inguinal node positive penile cancers: a single centre retrospective study

Penile cancer is a rare malignancy with limited evidence to guide management decisions. We present a large supra-network centre experience based on the management of 71 histologically confirmed inguinal node-positive penile cancer cases treated with radiotherapy with or without concurrent chemotherapy between 2002 and 2017.

Records of all cases who received radiotherapy to the inguinal/pelvic nodes as adjuvant treatment post-lymphadenectomy or as high-dose palliation for extensive/fixed nodes or extensive tumour were retrospectively reviewed and analysed. Primary outcome was overall survival while loco-regional relapse free survival was the secondary end-point of interest. Survival estimates were computed using Kaplan-Meier method with differences in survival assessed using the log-rank test.

Seventy one patients received radiotherapy either as adjuvant 50(70.4%) or high-dose palliative radiotherapy 21(29.6%). Median age at diagnosis was 59 years (32-82 years) while median follow-up was 56 months (12 to 178 months). Over the 15-year study period, 31 (43.7%) had evidence of a relapse, 34(47.9%) died while 37(52.1%) were alive at the end of the study period. Patients undergoing adjuvant radiotherapy (vs. palliative) had better overall (68.0% vs. 14.3%, $p<0.001$) and loco-regional relapse free (74.0% vs. 14.3%, $p<0.001$) survival. Those without extra capsular spread also had better survival while lack of margin positivity had non-significant effect on survival. Only 4 of 10(40%) patients who received additional chemotherapy were alive at the end of the study period

Adjuvant radiotherapy has a role post-lymphadenectomy; there is insufficient evidence to make definite conclusions regarding the use of additional chemotherapy due to the small numbers in this cohort. The In PACT study (International Penile Advanced Cancer Trial NCT02305654) has recently opened and will investigate the optimal sequencing of surgery, chemo-radiotherapy and chemotherapy in men with inguinal node positive penile cancer.

A11**Dr Rashmi Patel**

Academic Clinical Lecturer

Department of Psychosis Studies, IoPPN, King's College London

Negative symptoms and treatment outcomes in first episode psychosis: a natural language processing (NLP) electronic health record study.

Negative symptoms contribute towards substantial disability in people with schizophrenia. However, less is known about their impact compared to other symptom clusters in first episode psychosis (FEP). We sought to investigate how psychosis symptom clusters identified from a large electronic health record (EHR) dataset using natural language processing (NLP) were associated with psychiatric hospital admissions and antipsychotic treatment outcomes in people with FEP.

Data were obtained from pseudonymised EHRs of 1,835 adults with FEP using the Clinical Record Interactive Search tool (CRIS). Five psychosis symptom clusters (positive, negative, disorganisation, mania and depression) were identified using CRIS-CODE NLP software. Data on hospital admissions and antipsychotics prescribed in the 5 years following presentation were obtained. Their relationship with psychosis symptom clusters was analysed using multivariable negative binomial regression.

Mania (IRR 6.37, 95% CI 3.24 to 12.5) and positive symptoms (3.87, 1.98 to 7.58) were more strongly associated with increased hospital admission than disorganisation (1.68, 0.46 to 6.15), depression (1.55, 0.71 to 3.39) or negative symptoms (1.51, 0.51 to 4.48). Negative symptoms were more strongly associated with increased antipsychotic treatment failure (4.49, 2.35 to 8.59) than mania (3.65, 2.42 to 5.52), positive symptoms (3.35, 2.22 to 5.06), disorganisation (2.64, 1.23 to 5.68) or depression (2.18, 1.36 to 3.49).

Increased mania and positive symptoms predict more frequent psychiatric hospitalisation than negative symptoms. However, negative symptoms are more strongly associated with antipsychotic treatment failure than other symptom clusters. These findings highlight a need to develop better treatments for people with FEP who experience negative symptoms which appear to be less responsive to conventional antipsychotic treatment than other psychosis symptom clusters.

A12**Dr Tim Robbins**

PhD Student

University of Warwick / University Hospitals Coventry & Warwickshire NHS Trust

Demographic Determinants of Risk in Diabetes: Unlocking the Potential of Applied Data Analytics Research

Diabetes is a data rich pathology, with a wealth of readily extractable data stored on health record systems (EHRs). Linkage of patient level healthcare data, across health organisations, alongside matching with non-healthcare data is a key challenge to unlocking the potential of applied data analytics research. We demonstrate the linkage of healthcare data across inpatient, community and publically available data sources to understand demographic determinants of risk for patients with diabetes.

Data pre-specification was achieved through a systematic review of the medical & engineering research literature. Data was extracted from a tertiary referral centre EHR for all patients discharged with a diagnosis of diabetes over a 3 year period, this was linked with community results through a regional pathology network, alongside postcode-sector matching to socio-economic and national geographic data. Statistical analysis identified readmission risk factors for patients with diabetes.

Systematic review identified 47 unique readmission risk factors. Data was successfully extracted and linked for 23,307 patients, creating a unique high quality dataset of 10,281,406 values. This crosses primary care, secondary care, socio-economic & geographic sources. Initial analysis demonstrated statistically significant associations for risk factors related to patients with diabetes. An example being a statistically significant association between mortality following hospital discharge and deprivation level ($P < 0.01$). PROSPERO Review Registration and GAFREC Ethical Approval was secured in advance. Patients were involved in research question identification and research design, alongside creation of an innovative research ambassador recruitment strategy to support future studies.

Interrogation and linkage of the enormous amounts of healthcare data we store for patients has potential to both directly improve care and further our understanding of disease. The ongoing logistic regression modelling of this dataset, and application of machine learning methodologies, is enabling the creation of a unique risk stratification tool to better understand risk when patients are discharged from hospital with diabetes, thus demonstrating the clear potential of applied data analytics.

A13

Dr Lucy Stirland
Clinical Research Fellow
University of Edinburgh

"Old age doesn't come alone" – the value of involving a lay contributor in a PhD

Patient and public involvement (PPI) is increasingly important in clinical research settings, especially when using public and charitable funds. Many large trials now involve lay representatives, but there is less emphasis on PPI for researchers with smaller projects. My PhD is on the epidemiology of multimorbidity, polypharmacy and mental health in ageing, using large datasets. I aimed to involve a lay contributor in my PhD to relate this work to an individual older person's context.

With the help of a PPI Advisor, I wrote an "advert" describing my research and the lay involvement I envisaged. I found potential contributors through a local ageing research network and ethics approval was not required. My lay contributor, Mary, volunteered to meet every two months to discuss my research over coffee. She is 80 years old, has multimorbidity and takes multiple medications. She has consented to participate for the duration of my PhD and to being named.

Mary and I have been in contact since October 2017. We started by planning the lay contributor role together, then I summarised my PhD and introduced her to my supervisors. I share the results of my research with her and give feedback on conferences I attend. She highlights emergent issues that are important from a patient's perspective. We both participated in a priority setting partnership survey on multimorbidity in later life, and then analysed the top ten priorities that this process generated. We discuss relevant current affairs such as healthcare data privacy. Mary has given me her views on the content of a systematic review manuscript and reviewed the article's lay summary for readability.

I find Mary's input very valuable. It allows me to see my work from a different angle and through the eyes of an individual to whom it may be applied. This is particularly refreshing when working with big data. Mary says that "old age doesn't come alone", meaning that as she has aged, many symptoms and diagnoses seem to happen at once. She enjoys being involved with research and appreciates the fact that a researcher is interested in hearing the views of someone who receives healthcare.

A14

Dr Oliver Todd
Doctoral Research Fellow
University of Leeds/ Bradford Royal Infirmary

Optimising blood pressure in older people with frailty

It is currently unclear how we should best manage blood pressure treatment in the context of frailty. A key question is whether the degree of frailty should be taken into account during treatment decisions, rather than simply and solely the absolute level of blood pressure. For example, a more nuanced understanding might direct intensive therapy to older people in robust health, whilst being less intensive in the context of frailty. Such a strategy could minimise harm and maximise benefit.

We conducted a systematic review and meta-analysis of observational studies and investigate whether the association between blood pressure (BP) and clinical outcomes is different in older adults with and without frailty. PROSPERO Record CRD42017081635. Searched on 13.6.18. Reported clinical outcomes were compared by BP: categorically, according to systolic and diastolic thresholds defined by the American College of Cardiology (ACA) 2017 Joint Guidelines between frail and non-frail sub-groups.

Nine observational studies involving 21,906 older adults compared all-cause mortality over 6 years. Fixed effects meta-analysis of six studies demonstrated that in people with frailty, there was no difference in mortality between groups with a sBP less than 140 mm Hg compared with a sBP more than 140 mm Hg (HR 1.02, 95% CI 0.90 to 1.16). In the absence of frailty, a sBP lower than 140 mm Hg was associated with lower risk of death compared to a sBP more than 140 mm Hg (HR 0.86, 95% CI 0.77 to 0.96).

Evidence from observational studies demonstrates no mortality difference for older people with frailty whose systolic BP is less than 140 mm Hg, compared to those with a systolic BP more than 140 mm Hg. Observational studies support the application of current hypertension guidelines to older people without frailty. Their application to older people with frailty is of uncertain benefit.

Dr Gauri Verma

CT3 and Academic Clinical Fellow

Institute of Psychiatry Psychology and Neuroscience, Kings College London, South London and Maudsley NHS Foundation Trust

The role of the psychosocial environment in childhood on the developing brain and the risks of long term psychopathology amongst adults born very pre-term

This study investigates whether attachment and early psychosocial environment of adults born Very Pre Term (VPT) are associated with psychopathology, and structural brain changes. Evidence suggests the brain of those born VPT is vulnerable to changes in structural development, which might predispose to psychiatric illness. The developing brain is impressionable to early adversity. There is a link between attachment patterns and psychopathology and attachment patterns and brain development.

Methods:

- Cross-sectional study. Longitudinal component in analysis: MRI scans (ages 14, 18, 23 years) analysed to ascertain whether there are specific brain maturation patterns associated with psychiatric outcome at 30 years.
- Data collected: Early childcare environment, early adversity (Childhood experiences of Care and Abuse Questionnaire). Parent-peer attachment (Inventory of Parent Peer Attachment).
- Existing data: Voxel-based morphometry from MRI neuroimaging (ages 14, 18,23).

Findings:

- 66 participants - 20 controls. 46 preterm.
- Binary logistic regression analyses:
- Several types of adversity more common among individuals born preterm compared to controls. Associations failed to reach levels of statistical significance ($p > 0.05$). This is probably due to small numbers in our sample.
- Individuals born preterm were significantly more likely than controls to report having been bullied between ages 0-11 (45% vs 15%; OR=4.68, 95% CI 1.19-18.41, $p=0.027$).
- No significant difference in IPPA total score between preterm individuals and controls ($p=0.894$).
- No association between IPPA and total psychopathology within preterm individuals.

Interpretation:

Individuals born VPT were significantly more likely to have been bullied between 0-11 years of age.

There are no significant differences in adult attachment measures between VPT individuals and those born at full-term.

There are statistically significant differences in brain maturation patterns and early childcare amongst VPT.

A16 Dr Chris Wilkinson
MD student
University of Leeds

Sex differences in care provision and mortality for myocardial infarction

It is known that women have worse outcomes after acute myocardial infarction (AMI) than men. Reasons for this include differences in clinical presentation, underlying biology, care seeking and comorbidity profile, among others. There is also evidence that women less frequently receive optimal medical care. We investigated care provision using the European Society of Cardiology Acute Cardiovascular Care Association quality indicators to identify where deaths from AMI may be reduced in women.

Nationwide cohort study comprising 691,290 AMI hospitalisations in England and Wales (n=232 hospitals) from the Myocardial Ischaemia National Audit Project (a comprehensive registry of AMI hospitalisations mandated by the United Kingdom) between January 1, 2003 and June 30, 2013. Descriptive statistics and propensity score analysis were used to explore 30-day survival differences between men and women. Ethical approval was not required (secondary use of anonymised patient level data).

There were 34.4% (n=238,489) women (median age 76.7 [IQR 66.3 - 84.0] years; 33.9% [n=80,884] STEMI) and 65.5% (n=452,801) men (median age 67.1 [IQR 56.9 - 77.2] years; 42.5% [n=192,229] STEMI). Women less frequently received 13 of the 16 quality indicators compared with men including, timely reperfusion therapy for STEMI (76.8% vs. 78.9%; p<0.001), timely coronary angiography for NSTEMI (24.2% vs. 36.7%; p<0.001), dual anti-platelet therapy (75.4% vs. 78.7%), and secondary prevention therapies (87.2% vs. 89.6% for statins, 82.5% vs. 85.6% for ACEi/ARBs and 62.6% vs. 67.6% for beta-blockers; all p<0.001). Median 30-day GRACE risk score adjusted mortality was higher for women than men (5.2% (IQR 1.8% - 13.1%) vs. 2.3% (IQR 0.8% - 7.1%), p<0.001).

An estimated 8,243 (95% confidence interval 8,111 - 8,375) deaths among women could have been prevented over the study period if the provision of treatment had equalled that of men. According to these quality indicators for AMI, women in England and Wales less frequently received guideline-indicated care and had significantly higher mortality than men. Greater attention to the delivery of recommended AMI treatments for women has the potential to reduce the sex-AMI mortality.

A17 Dr Zenas Yiu
NIHR Doctoral Research Fellow in Dermatology
University of Manchester

Risk of Serious Infection Associated With Biologic Therapies in Psoriasis: Prospective Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR)

Patients with psoriasis are often concerned about the associated risk of serious infection with biologic therapies. The aim of this investigation was to identify whether individual biologic therapies have a higher risk of serious infection compared to non-biologic systemic therapies in plaque psoriasis patients using data from a large prospective United Kingdom and Republic of Ireland based pharmacovigilance registry (BADBIR) reflecting real-life clinical practice.

Etanercept, adalimumab, infliximab and ustekinumab were compared to non-biologics, inclusive of any exposure to methotrexate, ciclosporin, acitretin, fumaric acid esters, psoralen-ultraviolet A, hydroxycarbamide. Serious infection (SI) was defined by association with hospitalisation; use of intravenous antimicrobial therapy; and/or with death. Propensity-score weighted Cox proportional hazards models adjusted for a priori identified potential confounders were calculated for hazard ratios.

1352, 3271, 422 and 994 participants were included in the etanercept, adalimumab, infliximab and ustekinumab cohorts respectively and 3421 biologic-naïve participants were included in the non-biologic cohort. A total of 328 participants suffered a SI. No statistically significant increases in the risk of SI were observed for etanercept (adjusted hazard ratio [adjHR] 1.10; 95% CI 0.75 to 1.60); adalimumab (adjHR 0.93, 95% CI 0.69 to 1.26) or ustekinumab (adjHR 0.92, 95% CI 0.60 to 1.41) compared to non-biologics. Infliximab was associated with an increase in the risk of serious infection overall (adjusted hazard ratio (adjHR) 1.95, 95% CI 1.01, 3.75).

The risk of serious infection should not be a key discriminator for patients and clinicians when choosing between non-biologic systemic therapies, etanercept, adalimumab and ustekinumab for the treatment of psoriasis, but clinicians should take into account an increased risk of serious infection when considering infliximab.

Poster Competition - Group B

Dr Sarah Aitken

B1 Clinical Research Fellow
University of Cambridge

CTCF haploinsufficiency causes transcriptional dysregulation of cancer pathways

CCCTC-binding factor (CTCF) binds DNA to partition the mammalian genome into discrete structural and regulatory domains. CTCF is mutated in many human cancers and is implicated as a tumour suppressor gene. Although mouse models of Ctf haploinsufficiency are susceptible to spontaneous multi-lineage malignancies, the mechanism by which this occurs is unknown. Here, we exploit chronic Ctf hemizygoty to reveal its homeostatic roles in maintaining genome function and integrity.

Ctf^{+/-} mouse embryonic fibroblast (MEF) cultures were derived from Ctf heterozygous mice and corresponding Ctf^{+/+} homozygous lines from wild-type littermates. We applied RNA sequencing (RNA-seq), proteomics, chromosome conformation capture (HiC), and chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq) to decipher potential tumour suppressor mechanisms.

We find that Ctf hemizygous cells show modest but robust changes in almost a thousand sites of genomic CTCF occupancy; these are enriched for lower affinity binding events with weaker evolutionary conservation across the mouse lineage. Furthermore, we observe dysregulation of the expression of several hundred genes, which are concentrated in cancer-related pathways, and are caused by changes in transcriptional regulation. Chromatin structure is preserved but some loop interactions are destabilised; these are often found around differentially expressed genes and their enhancers. Importantly, the transcriptional alterations identified *in vitro* are recapitulated in mouse tumours and also in human cancers.

This multi-dimensional epigenomic profiling of a Ctf hemizygous mouse model system shows that chronic depletion of CTCF dysregulates steady-state gene expression subtly altering transcriptional regulation, including disruption of chromatin looping interactions. The transcriptional aberration of cancer pathways that we observed *in vitro* are also present in primary tumours, and we are now exploring how these chronic changes contribute to CTCF's tumour suppressor function.

Dr Peter Bailey

B2 Clinical Research Training Fellow
University of Cambridge

Mitochondrial lipoylation as a novel mechanism for regulating Hypoxia-Inducible Factors

Hypoxia-inducible factors (HIFs) regulate transcriptional responses to oxygen, but are also activated by metabolic signals, altering immune responses or promoting tumours. We previously identified a role for mitochondrial lipoylation, a poorly characterised post-translational fatty acid modification, in controlling HIFs independently of oxygen. Here, we identify a new gene, ABHD11, which controls the Krebs cycle through lipoylation, providing a novel link between fatty acid metabolism and HIFs.

To find genes which metabolically activate HIFs in aerobic conditions, we used a CRISPR/Cas9 genome-wide (176,500 sgRNA) forward genetic screen in human HeLa cells expressing a custom HIF-sensitive fluorescent reporter. Genes which when mutated led to HIF activation were enriched by fluorescence-activated cell sorting (FACS), and identified by high throughput sequencing. ABHD11 was identified as a top candidate gene, and its role in Krebs cycle function and the HIF response was explored.

We first validated that ABHD11, an uncharacterised mitochondrial hydrolase, led to stabilisation of HIF-1 α independently of oxygen using CRISPR/Cas9 depletion in multiple cancer cell lines. Mass spectrometry analysis of Krebs cycle metabolites demonstrates that ABHD11 depletion impairs oxidative phosphorylation by disrupting activity of the 2-oxoglutarate dehydrogenase complex (OGDHc) - a rate limiting step in the Krebs cycle that requires lipoylation. Biochemical and cell-based assays show that OGDHc function is lost following ABHD11 depletion due to a decrease in OGDHc lipoylation. ABHD11 loss prevents conjugation of a lipoate moiety on the catalytic subunit of the OGDHc, without affecting activity of other Krebs cycle enzymes.

We have identified ABHD11 as a new enzyme involved in metabolic activation of HIFs, Krebs cycle function and mitochondrial lipoylation. This work demonstrates fundamental insights into how HIFs can be controlled independently of oxygen, and provides a novel link between fatty acid metabolism and oxygen sensing pathways. We envisage that pharmacological targeting of lipoylation will be an important adjunct to drugs that will soon be in routine clinical use to target the HIF pathway.

B3 Mr Rahul Bhome
MRC Clinical Research Fellow
University of Southampton

Epithelial-mesenchymal transition status of colorectal cancer cells determines fibroblast phenotype by exosomal microRNA transfer

Colorectal cancer (CRC) mortality is largely attributed to metastasis. The stroma is critical in disease progression. Fibroblasts are the most abundant stromal cells, some of which display a myofibroblastic phenotype, which marks a poor prognosis. There is a histological association between myofibroblasts and mesenchymal carcinoma cells at the invasive front but the cause is unknown. Hence, we sought to investigate the role of epithelial-mesenchymal transition (EMT) on fibroblast phenotype.

CRC cell lines (DLD-1, HCT116, SW620 and SW480) were profiled for EMT markers by western blotting. Exosomes were isolated by differential ultracentrifugation and used to condition established and primary fibroblasts. TGF β -induced myofibroblast transdifferentiation was determined by α -smooth muscle actin (SMA) and fibronectin expression. Exosomal miRNAs were profiled by QuantimiR array and validated by qPCR. MiRNA mimics were then transfected into fibroblasts to recapitulate the findings.

SW480 cells expressed Zeb1, lacked E-cadherin and were considered mesenchymal, whereas DLD-1, HCT116 and SW620 expressed E-cadherin and were considered epithelial. Exosomes from these cells were shown to be 50-110 nm, with a lipid bilayer structure and enriched in Alix, TSG101, CD63 and CD81. Conditioning with epithelial but not mesenchymal exosomes (15 μ g/ml for 7 days) attenuated myofibroblast transdifferentiation when stimulated by TGF β (2 ng/ml for 72 h). Epithelial exosomes contained up to 20-fold more miR-200b/c than mesenchymal exosomes. Conditioning with epithelial but not mesenchymal exosomes increased cellular miR-200b/c levels in recipient fibroblasts 2-fold. Transfection of miR-200b/c mimics in fibroblasts similarly attenuated TGF β -induced transdifferentiation.

Here, we show that epithelial but not mesenchymal CRC cells, produce exosomes which are rich in miR-200b/c, which is deliverable to fibroblasts. Mir-200b/c repress Zeb1 in recipient fibroblasts, reducing their ability to acquire a myofibroblastic phenotype when stimulated by TGF β . Within the limitations of an in vitro system, we propose this as a novel mechanism to explain why myofibroblasts are scarce in the epithelial core of the tumour but more abundant at the mesenchymal invasive front.

B4 Mr James Blackmur
Clinical Research Fellow
University of Edinburgh

Vitamin D induces complex transcriptomic alterations in human normal rectal mucosa, implicating gene networks linked with carcinogenesis

The aetiology of colorectal cancer(CRC) includes genetic and environmental risk factors. Case-control studies demonstrate lower plasma vitamin D levels in people with previous CRC. Lower plasma vitamin D is associated with poorer CRC survival. However, supplementation studies have not demonstrated a preventative effect. In this human intervention study, we aimed to determine effects of vitamin D supplementation on the transcriptomic landscape of normal rectal mucosa and explore gene network effects.

After informed consent, rectal mucosa and blood was sampled from human subjects free from colorectal pathology (n=49). Participants received 3200IU daily oral vitamin D(Fultium-D3) and resampled after 12wks. Plasma 25OHD was assayed by mass spectrometry. RNA was extracted from rectal mucosa and the transcriptome assessed by paired-end total RNAseq. Vitamin D effect on gene expression was assessed using R package edgeR. Gene networks were analysed by WGCNA and functional annotation by clusterProfiler.

Plasma 25OHD increased in all participants(mean(SD)nmol/l:baseline 39.4(20.4), 12 wks 92.2(27.0), p<0.001; mean increase 52.8(28.3)). Fultium-D3 induced expression changes in 347 genes(203 up- and 144 down-regulated; FDR p<0.05). Co-expression network analysis identified 34 modules of highly correlated genes(genes within modules assumed to work cooperatively in related pathways). 1025 genes exhibited significant differences in expression interactions, of which 17 were also differentially expressed. 2 gene modules contained genes highly connected at baseline, but lowly connected at 12 weeks. 8 modules contained genes lowly connected at baseline but highly connected at 12wks. Overrepresented pathways in those 10 modules include focal adhesion, proteoglycans in cancer, and multiple immune pathways.

Pharmacologically-relevant doses of oral Vitamin D induce transcriptomic changes in normal rectal mucosa, the target tissue from which rectal neoplasia arises. Effects on gene expression & connectivity identify candidate genes underlying differences in transcriptional regulation. Functional annotation suggests involvement of multiple pathways, many linked to cancer formation. This human study provides novel insight into vitamin D response genes & pathways, potentially flagging effects on carcinogenesis

Dr James Fasham

B5

Academic Clinical Fellow

Royal Devon and Exeter Hospital / University of Exeter

Mutation in the intracellular chloride channel CLCC1 associated with autosomal recessive retinitis pigmentosa

Retinitis pigmentosa (RP) is an inherited eye disease characterised by photoreceptor death and retinal degeneration, resulting in vision loss. This condition affects ~1:4000 individuals worldwide and is highly clinically and genetically heterogeneous, presenting with variable symptoms and inheritance patterns. Our study investigates a novel, autosomal recessive cause of this condition

Affected individuals were identified in eight consanguineous families of Pakistani origin. A small region of shared homozygosity was identified in these families and this region was explored further by exome sequencing an affected individual. A mutation in CLCC1 (c.75C>A, p.D25E) was identified and its expression and function explored using cell lines, zebrafish and mouse models. Segregation of this mutation within affected families was performed and was consistent with phenotype.

We identified a homozygous missense variant (c.75C>A, p.D25E) in the CLCC1 gene, which encodes a presumptive intracellular chloride channel highly expressed in the retina, associated with autosomal recessive RP. The p.D25E alteration decreased CLCC1 channel function accompanied by accumulation of mutant protein in granules within the ER lumen. siRNA knockdown of CLCC1 mRNA induced apoptosis in ARPE-19 cells and TALEN KO in zebrafish was lethal 11 days post fertilization. There was depressed electroretinogram (ERG) cone response and cone spectral sensitivity of 5 dpf KO zebrafish and reduced eye size, retinal thickness, and expression of rod and cone opsins, which could be rescued by injection of wild type CLCC1 mRNA. *Clcc1*^{+/-} KO mice showed decreased ERGs and photoreceptor number.

Together these extensive genetic, clinical and functional datasets define a single founder gene mutation as a novel cause of RP in families of Pakistani descent, and strongly suggest that CLCC1 function is crucial for maintaining retinal integrity and function.

Dr Robert Gifford

B6

Clinical Research Fellow (PhD Student)

University of Edinburgh, Defence Medical Services

The endocrine effects of extreme exertion: an observational study of ovarian, bone and adrenal function in the first all-female Antarctic traverse

More adverse short-term exercise-associated reproductive, psychological and bone health-related outcomes have been reported in women than men, although the reasons for this are poorly understood. The first, all-female unassisted transantarctic ski expedition (Ex) provided a unique opportunity to perform an observational study aiming to characterise concurrent effects of extreme exercise (pulling an 80kg sledge 1700km) on hormonal axes relevant to reproductive dysfunction and related pathology.

Observational study in UK and Chile. All expedition members were eligible for inclusion. Pre- and post-Ex measures included metabolic, basal and dynamic endocrine (hypothalamic-pituitary-adrenal/gonadal (HPA/G) axes) and bone turnover markers (BTMs), anthropometry, and gold-standard body composition and bone micro-architecture imaging techniques. Primary outcomes were HPA/G and bone function change by repeated measures ANOVA. Ethical approval (827/MoDREC/16) and informed consent were obtained.

Six women (median (IQR) 32.7 (29.9-34.5) years) completed the Ex in 61 days. Mean (SD) weight loss was 9.37 (2.31) kg ($p < 0.0001$), comprising fat mass; lean mass was unchanged. Basal sex steroids, corticosteroids and metabolic markers were largely unaffected by the Ex, except leptin and vitamin D, which fell but recovered after 15 days ($p = 0.002$ and $p = 0.008$ respectively). LH reactivity was suppressed prior to and during the Ex, recovering after 15 days, while FSH was unchanged. Cortisol reactivity did not change during or after the Ex, although the HPA axis was sensitive to central suppression. Average monthly cortisol was elevated during the Ex. BTMs revealed uncoupling before and during the Ex, recovering after 15 days. Tibial fracture threshold and stiffness were unchanged after the Ex.

This study is unprecedented, demonstrating marked resilience in female HPA/G axes and bone health to extreme endurance exercise. Strengths include the high number of sensitive investigations and their proximity to the end of the expedition; weaknesses included the low 'n' and delay between study baseline and the expedition. Our findings imply sex differences in reproductive function, the HPA axis and bone need not preclude women from arduous exercise, given rigorous selection and training.

B7 Dr Nikki Hall
Clinical Lecturer & Honorary Ophthalmology Registrar
University of Edinburgh, Princess Alexandra Eye Pavilion

Whole genome sequencing analysis of a human "PAX6-negative" aniridia cohort

Congenital eye malformations cause 11% of UK childhood blindness. Aniridia is a panocular eye malformation characterised by aniridia (absence of the iris), foveal hypoplasia, glaucoma and keratopathy. Aniridia is strongly associated with heterozygous PAX6 loss: 90% of cases are caused by intragenic mutation of PAX6, or of its regulatory regions; 1% with FOX-C1/PITX2. We sought to identify new genetic causes of aniridia through whole genome sequencing (WGS) of a "PAX6-negative" aniridia cohort.

Consented classical aniridia cases with no genetic diagnosis were identified from the Human Genetics Unit eye malformation cohort. PAX6 Sanger sequencing was performed if previous screening was incomplete. Copy number variation (CNV) at the PAX6 locus was assessed by droplet digital (dd) PCR in a pilot subset. WGS was performed (BGI Hong Kong or Edinburgh Genomics UK), with relatives' DNA when available, followed by bioinformatic analysis and variant prioritisation. Approved by SE Scotland REC.

Forty three probands with classical aniridia were identified, of which 40 had sufficient quality gDNA to proceed. Sanger sequencing identified causative mutations in 3 cases (resulting in PAX6 p.R261X, p. R317X and p.L421Yfs*); ddPCR identified deletion of the PAX6 cis-regulatory SIMO element in a fourth case. The remaining cases (36 probands), with 2 affected relatives and 12 unaffected parents, underwent WGS (n=50) on Illumina HiSeq X, depth 30x. Analysis of the first batch (n=9) revealed a PAX6 splicing mutation (g.IVS3+1G>C) and allowed precise mapping of a known de novo t(1;9) translocation, whose causative role is under investigation. Ongoing analysis of the remaining WGS cohort, including trio-based analysis in 6 families, will be discussed.

In analysing WGS of one of the largest PAX6-negative aniridia cohorts yet assembled, this study provides the opportunity to identify novel aniridia loci or mutational mechanisms. As shown by results to date, apparent PAX6-negative cases may be caused by intronic splicing mutations or mutations in PAX6 cis-regulatory elements. Taking this and other recent research into account, we outline a suggested genetic investigation strategy for aniridia based on chromosomal array and gene panel testing.

B8 Miss Louise Hunter
Clinical Research Fellow
University of Manchester

Integration of genomic datasets provides insight into circadian regulation of glucocorticoid receptor action

Glucocorticoids (GCs) are potent anti-inflammatory agents. However, adverse effects, including derangement of hepatic metabolism, limit their use. Using RNA-sequencing in mice, we find that gene expression in liver is vastly more sensitive to the synthetic GC dexamethasone (DEX) during the day than at night. Now, we aim to gain mechanistic insight by profiling chromatin accessibility and glucocorticoid receptor (GR) binding genome-wide, and using bioinformatic tools to integrate datasets.

We treated C57BL/6 mice with DEX (or vehicle) in the middle of the day or night, and collected liver tissue, complying with the Animals (Scientific Procedures) Act 1986. We performed GR chromatin immunoprecipitation (ChIP) and assay for transposase-accessible chromatin (ATAC) plus DNA sequencing, following ENCODE guidelines (n >=2). We used MACS2 and csaw to find sites of open chromatin and of differential GR binding, then an original Python-based strategy to integrate these with RNA-seq data.

We found expression of 1,709 genes to be DEX-sensitive during the day, compared to only 211 at night. In parallel, 16,558 GR binding sites changed with daytime DEX administration, compared to 476 at night. Our Python-based method looked for enrichment of GC-regulated genes (over all genes in the genome) at defined distances from these GR binding sites. This revealed that, during the day, genes upregulated by DEX were closely related, by genomic distance, to DEX-sensitive GR binding sites. At night, this relationship extended to greater distances of over 1Mbp. Furthermore, at neither timepoint did we see enrichment of downregulated genes at any distance from DEX-sensitive GR sites. In contrast, genes regulated in both directions were strongly enriched near open chromatin.

We propose that daytime GC-sensitive genes are regulated by GR binding to proximal promoter and distal enhancer regions. At night, distal enhancers have greater prominence, implying that 3-dimensional reorganisation of the genome contributes to differential GC responses seen. The absence of a spatial relationship between GR binding and GC-downregulated genes, despite the presence of open chromatin, implies a distinct mechanism of action for GC-mediated repression, requiring intermediary factors.

Dr David Jeevan

B9

Wellbeing of Women Clinical Research Fellow
University of Birmingham & Pan Birmingham Gynaecology Cancer Centre

Unravelling the steroid metabolome in epithelial ovarian cancer

Ovarian tissue possesses the capacity for steroidogenesis from as early as seven weeks gestation. Perturbations in the steroidogenic pathways have been implicated in the development and progression of epithelial ovarian carcinoma in adulthood but the evidence has been limited. Analysis of RNA-seq data from ovarian tissue now allows the genes involved in these pathways to be studied comprehensively helping direct future investigations and highlighting possible mechanisms of this disease.

RNA-seq data from 293 serous epithelial ovarian carcinomas from The Cancer Genome Atlas were extracted and the genes involved in steroidogenesis were systematically interrogated for high and low expression. Pathway analysis confirmed significant findings. RNA-seq data from first trimester fetal ovary and healthy adult ovary were also compared.

Genes involved in the synthesis of androgens (HSD17B1, SRD5A1, AKR1C3, AR and STS) were all significantly upregulated in the epithelial ovarian carcinoma group when compared to normal healthy ovary (all $p < 0.05$). We are now working to demonstrate activity of the corresponding enzymes in established human ovarian cancer cell lines and human ovarian tumours.

Upregulated gene expression of the androgen synthesis pathway is associated with epithelial ovarian cancer but it is unclear if this is a mechanistic step in carcinogenesis or a feature of proliferation of tumour cells. Exploration of this unresolved question could yield diagnostic and therapeutic potential.

Dr Vikas Kaura

B10

MRC/BJA Clinical Research Fellow in Anaesthesia
University of Leeds

A Novel Knock-in Mouse Model of the Most Common Human Malignant Hyperthermia RYR1 Variant Exhibits Enhanced Sensitivity to RYR1 Agonists.

The human RYR1 variant c.7300G>A (p.G2434R) is the most common variant found in the UK Malignant Hyperthermia (MH) population [1]. It is classed as a weaker phenotype relative to other MH RYR1 variants and is the most common RYR1 variant to be associated with genotype-phenotype discordance [2]. We have generated a knock-in (KI) mouse line that expresses the isogenic mutation G2435R, and sought to characterise calcium responses to RYR1 agonists in primary myotubes derived from this KI mouse line.

Primary myoblasts were isolated from heterozygous RYR1G2435R/WT (HET) and homozygous RYR1G2435R/G2435R (HOM) and wild type (WT) mice. Myoblasts were differentiated into myotubes by withdrawal of growth factors. Myotubes from each genotype were loaded with fluo-4AM, and the changes in intracellular calcium (Ca^{2+}) in response to the RYR1 agonists caffeine, potassium chloride (KCl) and halothane were investigated using live-cell calcium imaging.

The EC50 (95% CI) for intracellular Ca^{2+} release in myotubes in response to caffeine significantly decreased from 5.7 (5.0-6.3) mM in WT, to 4.5 (3.9-5.0) mM in HET, and 1.8 (1.5-2.1) mM in HOM ($P < 0.0001$ one-way ANOVA, $n = 38-54$ myotubes per group). Similarly, the EC50 in response to KCl decreased from 21.4 (19.8-23.1) mM in WT, to 16.2 (15.2-17.2) mM in HET, and 11.2 (10.2-12.2) in HOM ($P < 0.0001$, $n=30-37$). Only HOMs had a significant response to 0.04mM halothane with Ca^{2+} transients of 12.7% (7.6-17.9) of the maximal KCl response, but both HETs and HOMs had a significantly greater response to 0.1 mM Halothane at 19.1% (12.4-25.7) and 63.1% (48.1-78.1) respectively, when compared to WT responses of 2.3% (1.2-3.3) and 3.2% (2-4.4) at 0.04 mM and 0.1 mM halothane ($P < 0.0001$, $n = 38-46$).

This study shows for the first time that the p.G2435R variant in the central domain of the RYR1 protein causes a significantly elevated sensitivity of myotubes to caffeine, K^{+} -induced depolarisation and halothane. This enhanced sensitivity exhibited a gene-dose effect and is consistent with *in vivo* data from this mouse [3]. The data from this novel MH mouse model parallel those observed in patients with the human RYR1 variant p.G2434R, thus providing a model for further mechanistic studies.

Dr Sam Khan

B11 ST3 Medical Oncology / Hope Against Cancer Clinical Research Fellow
University of Leicester / University Hospitals of Leicester

A single arm, open label preclinical study assessing the effects of curcumin on cancer stem-like cells using a novel 3D human colorectal cancer explant model

Over 25% of patients with colorectal cancer (CRC) present with metastatic disease for which the 5yr survival is 8%. Innovative prevention and treatment strategies to delay CRC are needed. Targeting cancer stem-like cells (CSCs) is an untapped strategy. Curcumin acts against CSCs via transcription factor Nanog. Nanog represents a therapeutic target specific to cancer and premalignant cells. A preclinical study using 3D explant models was designed to characterise the effects of curcumin on Nanog.

Patients (n=26) gave written informed consent to donate tissues prior to colorectal resection (REC approval: 14/WA/1166). Tissue collection, use and storage was carried out in accordance with ICH-GCP. Adenoma (n=5) and Dukes stage A-C (n=21) samples were studied as 3D explants. This included 15 male and 11 female samples with mean age 68 years and 57 years respectively. Tissues were dissected, cubed, explanted, treated with clinically achievable curcumin doses and treatment response analysed.

Following 24 hours exposure to curcumin (0-10uM) treatment response was assessed via CSC expression, proliferation, apoptosis and differentiation using immunohistochemistry or flow cytometry. A reduction in Nanog+ (mean 40%/SD 15.3%) and Nanog+Ki67+ (mean 80%/SD 17.0%) expression was observed in those who responded (16/20 clinical samples tested). No response identified in 4 samples. A reduction in Nanog with concurrent increase in differentiation was observed via IHC suggesting curcumin is able to push CSCs into a non-CSC phenotype. Patient derived CRC, adenoma or normal tissues were profiled for CSC expression (n=90). Nanog expression is significantly higher in adenoma (n=6) and CRC tissues (n=46) compared to normal tissues (n=38) ($p<0.0001$ or $p<0.001$ respectively using students T-test).

This is a small preclinical study using an explant assay. Data suggest Nanog is targeted by curcumin in adenoma or CRC tissues. Nanog may serve as a biomarker in clinical trials to identify CRC subtypes most amenable to curcumin treatment alone or in a combination treatment. This will help select individuals who are likely to benefit from curcumin as a cancer prevention and treatment agent. This concept may be applicable to the evaluation of novel agents for the treatment and prevention of CRC.

Dr Neelam Kumar

B12 NIHR Clinical Lecturer Respiratory Medicine
University College London

Loss of BAP1 function leads to TRAIL sensitivity in mesothelioma

Mesothelioma (MM) has no biomarker driven therapies. We used a drug screen of molecularly characterised MM lines to identify novel genomic biomarker driven therapy. This led to the discovery of a subset, defined by loss of function of the nuclear deubiquitinase BRCA associated protein 1 (BAP1), that demonstrate heightened sensitivity to TNF related apoptosis inducing ligand (TRAIL). We validated this across in vitro, in vivo and ex vivo models and delineated the underlying mechanism.

15 MM lines were molecularly characterised and screened for response to 94 compounds. The BAP1-TRAIL association was validated in 17 MM lines, 25 early passage MM cultures, mouse xenograft and human tumour explant models. Knock-in and knockout models in BAP1 mutant and wild type lines confirmed the effect. 6 mutant BAP1 constructs identified BAP1 sites that modulate TRAIL sensitivity. The effect of BAP1 function on the apoptosis pathway was determined using microarray and immunoblot analysis.

BAP1 LOF significantly correlated with TRAIL sensitivity in established MM lines ($p=0.015$) and primary MM cultures ($p=0.0064$). This association was confirmed in mouse xenograft ($p<0.05$) and tumour explant models. Mutagenesis of BAP1 confirmed deubiquitinase activity and its ability to bind to ASXL proteins to form the polycomb repressor deubiquitinase complex (PR-DUB) as determinants of TRAIL sensitivity, implicating modulation of transcriptional programmes as an underlying mechanism. Consistent with this, knockdown of ASXL1 also increased TRAIL sensitivity in MM lines and loss of BAP1 deubiquitinase and ASXL binding activity altered gene, and protein expression of components of the apoptotic machinery favouring apoptosis upon activation of death receptors.

We identify loss of BAP1 as a biomarker for TRAIL sensitivity in MM. BAP1 LOF is observed in 67% of MM and BAP1 immunohistochemistry in use as a diagnostic tool. TRAIL has shown tolerability in phase I/II trials of unselected populations (no MM trials). Hence this approach is ready for actionable clinical use. The strength of the study is the extensive validation in multiple MM models. The main weakness is a lack of validation in a clinical cohort. Confirmation in a clinical trial is a priority.

Dr Fraser Millar

B13 ECAT Wellcome Trust Clinical Research Fellow
University of Edinburgh

Toll-like receptor 2 signalling is integral in the oncogenic Ras mediated senescence associated secretory phenotype

Oncogene induced senescence is an innate tumour suppressor mechanism instigated following oncogene activation. Senescent cells secrete an array of proteins that constitute the senescence associated secretory phenotype (SASP) which function to reinforce senescence, induce paracrine senescence and recruit immune cells resulting in senescent cell clearance. Recent data has shown that following oncogenic RAS activation in vitro, toll-like receptor 2 (TLR2) signalling is integral in SASP expression.

Hydrodynamic delivery of NRasG12V-IRES-GFP plasmid with CMV-SB transposase encoding plasmid was performed in wild-type and Tlr2^{-/-} C57BL/6 mice. Plasmid encoding an effector loop mutant (NRasG12V/D38A) was used as a control. After 6 days mice were culled and liver tissue was harvested. Stable expression of our construct was determined by immunohistochemical staining for NRas and GFP. RNA was extracted from snap frozen liver samples and SASP expression was measured using qRT-PCR.

NRas and GFP staining was evident throughout liver sections indicating efficient delivery of our mutant NRas constructs. Significant upregulation of the SASP factors IL-1 α , IL-1 β and IL-6 was evident in wild-type mice receiving NRasG12V constructs compared to those receiving NRasG12V/D38A constructs (n=3, p=0.0424, p=0.005 and p=0.0036 respectively). In Tlr2^{-/-} mice receiving NRasG12V constructs, IL-1 β expression was significantly decreased compared to wild-type mice (n=3, p<0.02). IL-1 α and IL-6 was also reduced (p=0.0526 and p=0.0857 respectively).

We have shown preliminary in vivo data indicating that Tlr2 contributes to the expression of IL-1 β which is integral to the SASP following oncogene activation. Understanding the mechanisms regulating SASP expression is of significant clinical interest given the importance of the SASP in tumour suppression. Further work assessing the effect of Tlr2 signalling on tumour burden will provide insight into the potential therapeutic benefits of targeting this signalling pathway.

Dr Louise Porter

B14 NIHR ACL in Ophthalmology
University of Liverpool

The SKI, GTF2H4 and TNXB genes are differentially methylated and expressed in the retinal pigment epithelium of individuals with age-related macular degeneration

Age-related macular degeneration (AMD) is a degenerative retinal disorder and the foremost cause of blindness affecting ageing populations. The genetic basis of AMD is well understood but no treatments exist for the most prevalent dry forms of the disease affecting 90%. Therefore, epigenetic mechanisms of gene regulation are of considerable interest in AMD. We investigate DNA methylation changes in dry AMD and investigate whether DNA methylation may underlie differential gene expression in AMD.

We performed genome-wide DNA methylation analysis of 44 human retinal pigment epithelium (RPE) samples from donors with AMD and controls (Illumina Human Methylation 450k BeadChip array) then bisulphite pyrosequencing on validation sets of 55 RPE/choroid samples from AMD donors and controls including biological (n=17) and technical replicates (n=38). Quantitative RT-PCR was performed on independent donor RPE samples (n=8) to associate DNA methylation changes with local gene expression profiles.

We identified differential methylation of SKI (p=1.18x10⁻⁹), GTF2H4 (p=7.03x10⁻⁷), and TNXB (p=6.30x10⁻⁶) genes in early and intermediate AMD and validated these changes in 55 RPE samples using bisulphite pyrosequencing. No evidence of widespread global DNA methylation aberrations were present in AMD using LINE-1 analysis. We then associated DNA methylation changes with differential regulation of implicated genes in the RPE mRNA of independent AMD donors confirming gene expression differences at these genes. The differentially methylated targets SKI and GTF2H4 regulate disease pathways implicated but understudied in AMD including TGF beta signalling (SKI), and transcription dependant DNA repair mechanisms (GTF2H4). TNXB has been previously associated with AMD through GWAS studies.

DNA methylation changes in individual genes SKI, GTF2H4 and TNXB associated with gene expression changes implies that their expression may be regulated in the disease context by DNA methylation, and that they may play important roles in the RPE in AMD. Absence of widespread DNA methylation changes confirms that differences observed are not due to global DNA methylation aberrations. Identification of novel targets is an important finding as DNA methylation may be altered therapeutically.

B15 Dr Claire Rooney
Specialty Registrar, Respiratory Medicine
Kings College London / University of Glasgow

Targeting CD98hc in Malignant Mesothelioma

Malignant mesothelioma (MM) is a uniformly fatal cancer caused by asbestos exposure. It is characterised by a highly pro-inflammatory microenvironment, contributing to tumour initiation and progression. CD98hc, an integrin binding glycoprotein, is overexpressed in other cancers and is implicated in this process. This study examines CD98hc expression in human MM tissue microarray samples and tests the effect of genetic and pharmacological CD98hc inhibition on mesothelioma growth in vivo.

CD98hc expression was examined by IHC in 42 human MM tissue samples, scored and correlated to clinico-pathological data. Tumour specific effect was shown by creating a doxy-inducible CD98hc shRNA human MM cell line, injected into the flanks of NSG mice. Additionally, in a syngeneic model murine MM cells were grown in BalBC/Ola mice and treated daily with an intraperitoneal CD98hc inhibitor. Tumour burden was measured using calipers and tumours were excised for histological and RNA analysis.

Survival analysis revealed poorer OS in MM patients with 'high' vs 'low' CD98hc status ($p = 0.04$). In Cox modelling 'low' CD98hc status was an independent predictor of 1 year survival (HR 2.93 (1.9-6)) when adjusted for histopathological subtype. In vivo, human tumour growth was abolished in 'early' CD98hc knockdown vs controls (vol. $136.56\text{mm}^3 \pm 18.42$ and 44.36 ± 6.36 , $p < 0.001$) and reduced by 53% in 'late' CD98 KD tumours (vol. $136.56\text{mm}^3 \pm 18.42$ and 72.1 ± 4.22 , $p < 0.001$). Inhibiting CD98hc in the syngeneic model was similarly effective (vol. $181\text{mm}^3 \pm 27$ vs 77 ± 16.6 , $p < 0.001$). IHC analysis shows reduced proliferation/ increased apoptosis. The syngeneic model suggests additive mechanisms mediated by loss of M2 macrophage polarisation and an increase in tumour infiltrating lymphocytes.

We demonstrate that CD98hc is indeed over-expressed in human MM. Furthermore 'high' CD98hc expression status is shown to be a negative prognostic factor. In vivo studies demonstrate a key role for CD98hc as a regulator of tumour growth, both directly and in crosstalk with the immune microenvironment. Thus, CD98hc is potentially both an important clinical marker in MM and a rational treatment target. This makes a convincing argument for developing CD98hc inhibitors in malignant mesothelioma.

B16 Dr Giacomo Rossitto
Clinical Research Fellow
University of Glasgow

Tissue Sodium is A Highly Sensitive Marker of Subclinical and Localised Oedema

At variance with the classic physiology concepts, hypertonic Na^+ accumulation has been shown to occur in peripheral tissues where lymphatic vessels act as a buffering system and glycosaminoglycans (GAGs) as binding site. In humans, higher ^{23}Na MR signal from skin and skeletal muscle has been associated with aging, hypertension and diabetes, but its water independent nature is debated. This study explores Na^+ myocardial accumulation in a rat model and, by theoretical modelling, in general tissues.

Heart samples from hypertensive young and old rats (SHRSP) and normotensive age matched controls (WKY) were used for chemical analysis of tissue Na^+ and K^+ content by flame photometry, gravimetric measurement of water content, as the difference between wet and dry weight and histologic quantification of interstitial GAGs by alcian blue. A model for prediction of chemical composition of tissues, as a function of extracellular volume fraction (ECV%) and its change in oedema, was developed

Interstitial GAGs in the myocardium increase with aging and hypertension. Myocardial Na^+ content and concentration increase in SHRSP old compared to SHRSP young and age matched WKY (0.19 ± 0.04 , 0.13 ± 0.01 , 0.14 ± 0.03 mmol/gDW and 54.5 ± 4.1 , 45.8 ± 5.5 , 46.6 ± 3.6 , mmol/l, respectively), paralleled by an increase in water (76.7 ± 0.9 vs 74.4 ± 1.0 and 73.5 ± 1.5 %wet weight, respectively). K^+ concentration shows a mirror pattern decrease. According to the model, total Na^+ concentration is expected to be higher with increasing tissue ECV%; the opposite happens to K^+ . Remarkably, the proportional increase in Na^+ content due to different degrees of oedema is up to 3.5 times higher than the increase in water content, in particular in tissues with low ECV% (such as myocardial or skeletal muscle).

Na^+ accumulates in the myocardium, but paralleled by water: this suggests tissue oedema. Of note, Na^+ is intrinsically more sensitive than water to detect oedema. It is likely that isotonic, rather than hypertonic, Na^+ accumulation occurs with aging and CV disease in most tissues. Therefore, tissue Na^+ analysis has broad potential for early diagnosis of subclinical and localised oedema. Its link with lymphatic function in heart failure is under investigation in a clinical study (ref.GN17CA152).

B17 Dr Claire Salter
ACF Clinical Genetics
University of Exeter

Exploring the neuropathological outcomes associated with different classes of choline transporter mutation

SLC5A7 encodes the pre-synaptic choline transporter (CHT) essential for normal acetylcholine signalling at peripheral and central cholinergic synapses, including the neuromuscular junction (NMJ). We have clinically and molecularly defined two distinct neurological conditions resulting from autosomal dominant and recessively-acting pathogenic variants in SLC5A7.

Phenotyping: The autosomal dominant condition comprises an adult-onset distal hereditary motor neuropathy (dHMN) with variable features including vocal cord paresis and pyramidal signs. In contrast, the recessive condition comprises a more severe outcome of congenital myaesthetic syndrome (CMS). Genetic studies: Whole exome sequencing in family members and confirmation of variants by dideoxy-sequencing. Functional studies: Assessment of CHT activity and localisation in cells and *C. Elegans*.

The pathogenic variants identified to underlie the dHMN-phenotype are predicted to cause truncation of the proteins highly conserved cytoplasmic tail, whilst those underlying the CMS-phenotype are missense located outside the proteins tail. Cells transfected with CHT construct harbouring the dHMN-nonsense mutations revealed a significant reduction in choline transporter activity. This fell further when co-expressed with wild-type CHT, suggesting a dominant-negative mechanism. Transporter activity fell to near undetectable levels in cells transfected with CHT construct harbouring the CMS-missense mutations, and an additional reduction in CHT transport to the cell surface was observed. Further studies of the recessively-acting mutations in *C. Elegans* confirmed the transport abnormalities.

These findings demonstrate the central role of CHT in acetylcholine neurotransmission and display the synapse's innate sensitivity to changes in transporter activity. Our studies have determined that dominant and recessively-acting CHT mutations lead to variably impaired CHT functionality, through alterations in CHT activity and protein transport to the NMJ, leading to distinct clinical outcomes with important implications for diagnosis and personalised treatment provision.

B18 Dr Adam Sharp
Medical Research Clinical Research Training Fellow
Institute of Cancer Research

Novel strategies to target RNA splicing to overcome androgen receptor splice variant-7 (AR-V7) signalling in castration resistant prostate cancer (CRPC).

Generation of constitutively active androgen receptor splice variant-7 (AR-V7) by aberrant RNA splicing drives persistent androgen receptor (AR) signalling in castration resistant prostate cancer (CRPC). No current therapies target AR-V7 and an attractive strategy is to inhibit RNA splicing. Here we present inhibition of the bromodomain and extra-terminal (BET) family proteins and splicing factor-B (anonymised; Sf-B) as novel approaches to suppress RNA splicing and AR-SV generation in CRPC.

The clinical importance of AR-V7, BET family proteins and Sf-B were determined from RNA-seq and immunohistochemistry analysis of CRPC biopsies. The effect of BET inhibition (BETi), BET family protein knockdown and Sf-B protein knockdown on AR-V7 generation, AR signalling and growth in patient derived CRPC models was determined. Sf-B was identified as a critical splicing factor for AR-V7 generation in a focused siRNA screen of common splicing factors.

AR-V7 protein associates with resistance to endocrine therapies. BRD2, BRD3 and BRD4 RNA expression correlates with AR signalling in CRPC biopsies. Chemical BET inhibition (BETi) and protein knockdown reduced AR-V7 expression, AR signalling and PC model growth. Mechanistically, BETi regulates RNA splicing and AR-V7 expression. Despite these data, the pleiotropic effects of BETi raises concerns about treatment related toxicities. In light of this, we identified Sf-B, a critical splicing factor for BETi mediated AR-V7 regulation. We demonstrate Sf-B is key to RNA splicing, AR-V7 generation and PC cell growth. In addition; Sf-B expression associated with reduced clinical benefit from current endocrine therapies.

Firstly, AR-V7 emerges as patients develop CRPC and associates with reduced clinical benefit from endocrine therapies. Secondly, we identify AR-V7 to be generated by aberrant RNA splicing; inhibition of which provides an attractive therapeutic strategy to prevent AR-V7 generation in lethal PC. Consistent with this, we show that inhibition of RNA splicing through regulation of BET family proteins and Sf-B provides novel approaches to target AR-V7 positive CRPC and warrants further investigation.

B19

Mr Peter Vaughan-Shaw

ECAT SCREDS Clinical Lecturer & Honorary StR in Colorectal Surgery
University of Edinburgh

Interaction between genetic variation at chr16q22 and plasma vitamin D influences CDH1 expression in large bowel epithelium which may explain some of the missing heritability of colorectal cancer

Lower plasma vitamin D level is associated with increased colorectal cancer (CRC) risk in epidemiological studies and genetic variation at chr16q22.1 influences this association. The chr16q22.1 SNP (rs9929218) lies intronic to the CDH1 gene and exerts a main effect on CRC risk (OR=1.1; P=1.2e-8). We hypothesise that vitamin D influences CDH1 expression in normal colorectal epithelium through gene-environment (GxE) effects mediated by the vitamin D receptor (VDR) and FOXO transcription factors.

Ten CRC cell lines were treated with calcitriol (0.5-100nM; 16hrs) and RNA harvested. Normal colorectal mucosa and blood were sampled from 424 human subjects for correlative analysis. Intervention subjects (n=50) underwent rectal biopsy before, during, after 12wks oral vitamin D3 (3200IU/day). Gene expression analysis (qRT-PCR, microarray), plasma 25OHD assay (LC-MS) and genotyping (microarray) were performed. T-test and interaction tests were run, ethical approval and informed consent obtained.

In vitro studies: Calcitriol induced differential expression of 30 genes (paired T-test FDR P<0.05), with CDH1 the top hit. A GxE interaction between CDH1 induction, rs9929218 genotype and calcitriol concentration was observed (ANOVA interaction test R²=0.66; P=0.037). Human correlative study: Expression of CDH1 and VDR were highly correlated (R=0.75; P=1.01e-74). A strong interaction effect (R²=0.70; P=3.57e-07) between CDH1 expression, rs9929218 genotype and expression of VDR, FOXO and SIRT1 (a FOXO regulator) was seen. Human intervention study: supplementation increased 25OHD (Δ 3.00; P=2.5e-09) and induced rectal mucosa CDH1 expression (Δ 1.22; P=0.01) with strong GxE interaction effect between 25OHD increment, induction of CDH1, and VDR, FOXO, SIRT1 (R²=0.90; P=0.0007). No SAE occurred.

CDH1 expression is modified by strong GxE effects involving the CRC susceptibility locus chr16q22.1 and vitamin D. FOXO transcription factors modulate the GxE, supporting a proposed model of ligand dependent regulation of FOXO by VDR and transcription activation of CDH1 by the FOXO complex dependent on rs9929218 genotype. These data support rectal CDH1 expression as an intermediate biomarker for vitamin D chemopreventive studies and suggest GxE underlie some of the missing heritability of CRC.

Poster Competition - Group C

C1 Dr Helen Alexander
Clinical Research Fellow
King's College London

The role of *Staphylococcus aureus* and the skin commensal microbiome on immunological responses in atopic dermatitis

S. aureus (SA) is known to play an important role in atopic dermatitis (AD). Disease flares are associated with SA skin infection, and SA abundance correlates with flare and disease severity. Importantly, however, the extent to which SA is causative rather than a bystander of the inflammatory AD skin environment is not clear. If SA does have a causal role, the mechanisms through which it exerts its function on the skin immune system to drive inflammation are also not fully understood.

This study aims to investigate the role of SA and commensal bacteria in AD pathogenesis through analysis of the skin metagenome and transcriptome. Skin microbiome samples and underlying skin biopsies were obtained from adults with mild-severe AD (n=88), and healthy subjects (n=117). The metagenome was sequenced to quantify microbial abundance by aligning metagenome reads to species-specific markers. SA virulence factor gene abundances were measured by mapping metagenome reads to gene sequences.

There are clear differences in the microbiome between AD and healthy volunteers with increased SA and reduced commensals in AD. SA abundance correlates with AD severity. The data reveal a subset of AD patients whose microbiome is heavily dominated by SA. The SA virulence factor delta-toxin genes are present in a significantly higher proportion of AD samples compared to healthy volunteers.

This work demonstrates that our methodology detects expected differences between AD patients and healthy controls. The subset of AD patients whose microbiome is heavily dominated by SA will be interrogated further to identify specific SA strains and virulence genes in AD. The AD host transcriptome profile associated with SA and commensal bacteria will be explored to reveal potential microbe-host interactions. These interactions may provide novel therapeutic targets for the disease.

C2 Dr Hussein Al-Mossawi
NIHR Academic Clinical Lecturer
University of Oxford / Nuffield Orthopaedic Centre

Context-specific regulation of monocyte surface IL7R expression and soluble receptor secretion by a common inflammatory disease risk allele

Interleukin 7 (IL-7) plays a key role in T cell survival and proliferation and its biological effects are modulated by the soluble form of the IL-7 receptor (IL7R) which has been shown to prolong its activity in inflammation. Polymorphisms of the IL7R are associated with multiple inflammatory diseases including ankylosing spondylitis. IL7R mRNA is induced in stimulated monocytes in a genetically determined manner, yet a role for IL7R in monocyte biology remains unexplored.

Protein expression of IL7R on monocytes was measured in by flow cytometry in the context of innate immune activation with LPS or TNF in a cohort of volunteers recruited from the Oxford biobank. Individuals were genotyped post-analysis and genotype associated with surface IL7R. Soluble IL7R was quantified by ELISA in purified monocyte cultures stimulated with LPS and correlated with genotype. Single cell RNA sequencing was performed on synovial monocytes of patients with spondyloarthritis.

Monocyte surface and soluble IL7R protein are markedly expressed in response to lipopolysaccharide (LPS) and alleles of rs6897932, a non-synonymous IL7R polymorphism associated with susceptibility to Multiple Sclerosis and spondyloarthritis, are the key determinant of both surface and soluble IL7R in the context of inflammation. No effect of this allele was observed in unstimulated monocytes and across lymphoid subsets. Stimulated monocytes were sensitive to exogenous IL-7, which elicits a defined transcriptional signature. Flow cytometry and single cell sequencing of synovial fluid monocytes from patients with spondyloarthritis showed an enlarged subset of IL7R+ monocytes with a unique transcriptional profile that markedly overlapped the in-vitro IL-7 induced geneset.

These data demonstrate disease-associated genetic variants at IL7R specifically impact monocyte surface and soluble IL7R following innate immune stimulation, suggesting a previously unappreciated key role for monocytes in IL-7 pathway biology and IL7R-associated diseases.

C3 Dr Kenneth Baker
NIHR Clinical Lecturer in Rheumatology
Newcastle University

Predictors of drug-free remission in rheumatoid arthritis: results from the prospective Biomarkers of Remission in Rheumatoid Arthritis (BioRRA) Study

Remission is now an achievable target in rheumatoid arthritis (RA) using disease-modifying anti-rheumatic drugs (DMARDs) prescribed in modern treat-to-target regimens. However, DMARDs carry potential side-effects, and require expensive and intrusive safety monitoring. Half of patients can maintain remission following DMARD cessation, but this cannot be reliably predicted. We aimed to identify biomarkers to predict drug-free remission (DFR) in RA through a prospective study of DMARD cessation.

Patients in established RA remission stopped DMARDs and were monitored for 6 months. The primary outcome was time-to-flare (TTF), defined as DAS28-CRP (disease activity score in 28 joints C-reactive protein) \geq 2.4. Baseline clinical/ultrasound measures, serum cytokines, and peripheral CD4+ T cell gene expression were assessed to predict TTF and DFR by Cox regression and receiver-operating characteristic (ROC) analysis. NHS REC approval and written consent obtained. Registration: NCT02219347.

23/44 (52%) patients experienced an arthritis flare at a median (IQR) of 48 (31.5 - 86.5) days following DMARD cessation. There were no serious adverse events. A composite score incorporating five baseline variables (three genes [FAM102B, ENSG00000228010, ENSG00000227070], one cytokine [interleukin-27], one clinical [ACR/EULAR Boolean remission], no ultrasound) differentiated future flare and DFR with an area under the ROC curve of 0.96 (95% CI 0.91-1.00), sensitivity 0.91 (0.78 - 1.00) and specificity 0.95 (0.84 - 1.00).

This study provides proof-of-concept evidence for the existence of biomarkers of DFR in RA. We present an unprecedented scope of analysis over multiple biomarker domains; limitations include a small study size and short duration of follow-up. If validated in an external cohort, these biomarkers may hold promise in guiding DMARD withdrawal with consequent minimisation of medication adverse events, healthcare costs, and restoration of patients' normal lifestyles.

C4 Dr Faye Cooles
NIHR Clinical Lecturer and Rheumatology Speciality Trainee (Registrar)
Newcastle University and Northern Deanery

The interferon gene signature is increased in early drug naïve rheumatoid arthritis and predicts a poorer response to initial therapies

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease of unknown aetiology with significant morbidity. Approximately 20% of established RA patients have a positive whole blood interferon gene signature (IGS). While this does not correlate with disease activity, it does impact on response to certain therapies. The IGS is modulated by glucocorticoids which can be a confounder when examining established RA. We therefore wished to examine the prevalence and prognostic value of the interferon gene signature (IGS) in early glucocorticoid and therapy naïve RA (eRA).

eRA patients were recruited at diagnosis. Clinical parameters, including disease activity, were recorded at baseline and again at 6 months along with treatment history. Established disease (RA and SLE; disease duration >12 months) and healthy controls (HC) were recruited. Whole blood RNA expression of 5 IGS genes (MxA, IFI6, OAS1, ISG15, IFI44L) was quantified and the mean termed the IGS. This was "positive" when \geq 2 SD above HC values. Some eRA patients had IGS repeated at 6 months. Statistical analysis used JMP Statistical Visualization Software v 11. Significance when $p < 0.05$.

50 DMARD naïve early RA patients, 23 established RA patients, 23 SLE patients and 23 healthy controls were recruited. Both RA cohorts were matched for inflammatory markers and age/sex however all analyses were corrected for age/sex. Twice as many early RA patients as established RA patients exhibited an IGS (42% vs 21%). There was significantly up regulated expression of interferon signature genes ($p < 0.01$) to levels reached in SLE. However eRA IGS expression fell between baseline and 6 months ($p < 0.05$) even when patients with additional glucocorticoid administration were excluded. The eRA baseline IGS score significantly associated with DAS-28 both at baseline and 6 months (multiple regression, $p < 0.05$ and $p < 0.005$). It also predicted poorer response to initial therapies and increased glucocorticoid requirements at 6 months (ordinal and nominal regression, $p < 0.05$ and $p < 0.001$ respectively).

We examined for the first time the IGS in eRA and show the IGS is increased and has prognostic value. Early disease control is crucial to modify long-term morbidity and these findings could ultimately inform management and therapeutic stratification, e.g. early use of JAK inhibitors which affect type 1 interferon signalling. We were not able to identify any individual effects of early treatments on the IGS due to our cohort sizes, however further work is on going to both expand and validate findings as well as elucidate a potential mechanism for this effect, i.e. epigenetic modifications.

C5 Dr Adam Croft
NIHR Clinical Lecturer
University of Birmingham

Pathologically distinct fibroblast subsets drive inflammation and tissue damage in arthritis

The identification of lymphocyte subsets with non-overlapping effector functions has been pivotal to the development of targeted therapies in immune mediated inflammatory diseases (IMIDs). Yet, despite their key role in disease, it remains unclear whether fibroblast subclasses with non-overlapping functions also exist and are responsible for the wide variety of tissue driven pathologies observed in IMIDs such as inflammation and damage.

The KRN serum transfer (STIA) model of experimental arthritis was used to investigate the effect of fibroblasts on inflammation. Single cell RNA sequencing was performed using 10x Chromium technology on the CD45 negative cell fraction of digested synovial membrane from inflamed mouse joints. We utilized a transgenic mouse in which FAP expressing cells were conditionally ablated by administration of diphtheria toxin. Damage was determined by microCT analysis and histology.

We identify and describe the biology of distinct subsets of fibroblasts responsible for mediating either inflammation or tissue damage in arthritis. We show that deletion of FAP+ synovial cells suppressed both inflammation and bone erosions in murine models of resolving and persistent arthritis. Single cell transcriptional analysis identified two distinct fibroblast subsets: FAP+ THY1+ immune effector fibroblasts located in the synovial sub-lining, and FAP+ THY1- destructive fibroblasts restricted to the synovial lining. When adoptively transferred into the joint, FAP+ THY1- fibroblasts selectively mediate bone and cartilage damage with little effect on inflammation whereas transfer of FAP+ THY1+ fibroblasts resulted in a more severe inflammatory arthritis but little effect on damage.

Our findings describing anatomically discrete, functionally distinct fibroblast subsets with non-overlapping functions have important implications for cell based therapies aimed at modulating inflammation and tissue damage.

C6 Dr Kristen Davies
Academic Foundation Year 1 Doctor
Northumbria Specialist Emergency Care Hospital

Fatigue In Primary Sjögren's Syndrome (pSS) Is Associated With Lower Levels Of Proinflammatory Cytokines: A Validation Study

Fatigue is a complex and disabling symptom which is a prominent feature of number of chronic diseases such as the autoimmune disease Primary Sjögren's syndrome (pSS). It has previously been thought that proinflammatory cytokines can drive fatigue. Previous work by our group has suggested that certain pro-inflammatory cytokines are inversely related to patient-reported levels of fatigue in pSS. To date, these findings have not been validated. This study aims to validate this observation.

Blood levels of seven cytokines were measured in 120 patients with pSS from the United Kingdom Primary Sjögren's Syndrome Registry and 30 age-matched healthy non-fatigued controls. Patient-reported scores for fatigue were classified according to severity and compared to cytokine levels using analysis of variance. The differences between cytokines in cases and controls were evaluated using Wilcoxon test. A logistic regression model was used to determine the most important predictors of fatigue.

Five cytokines, interferon- γ -induced protein-10 (IP-10), tumour necrosis factor- α (TNF α), interferon- α (IFN α), interferon- γ (IFN- γ), and lymphotoxin- α (LT- α) were significantly higher in patients with pSS (n=120) compared to non-fatigued controls (n=30). Levels of two pro-inflammatory cytokines, TNF α (p=0.021) and LT α (p=0.043), were inversely related to patient-reported levels of fatigue. Cytokine levels, disease-specific and clinical parameters as well as pain, anxiety and depression were used as predictors in our validation model. The model correctly predicts fatigue levels with 85% accuracy.

Consistent with the original study, pain, depression, and proinflammatory cytokines appear to be the most powerful predictors of fatigue in pSS. TNF- α and LT- α have an inverse relationship with fatigue severity in pSS challenging the notion that proinflammatory cytokines directly mediate fatigue in chronic immunological conditions.

C7**Miss Grace Edmunds**Veterinary Research Training Fellow
University of Bristol**Dual targeting of Adenosine and TIM3 produces synergistic improvement in anti-tumour immunity in a murine model of Renal Carcinoma. A pre-clinical study.**

CD8+ Cytotoxic T Lymphocytes (CTL) are able to kill tumour cells. However, their killing is suppressed within the tumour microenvironment. The interaction of immune checkpoint receptors on CTL, with tumour-derived ligands mediates such suppression. Drugs which block checkpoints have shown great promise and control tumour growth. However, there is a high rate of immune adverse effects associated with these drugs. Moreover, in response to blockade of one receptor, tumours may acquire resistance by upregulating other checkpoints. There is a need to identify novel tumour-specific checkpoints to reduce side-effects and prevent tumour immune evasion.

BALB/c mice bearing subcutaneous murine renal carcinoma, expressing haemagglutinin (RencaHA) were treated as follows: a) Adoptive transfer with primed TcR transgenic, HA-specific CD8+ T cells (CL4 cells) b) A2a Adenosine Receptor (AR) antagonist 200ug, I.P. q2d c) Anti-TIM3 mAb (Clone RMT-3, BioXcell), 100ug/kg, I.P. q2d. Tumour growth was measured and the volume calculated (Volume = $0.5 \times (\text{Length} \times \text{Width}^2)$). Flow cytometric analysis of checkpoint expression was carried out using BD Fortessa, FACS DIVA and FlowJo (Treestar). Statistics were performed using SPSS statistics and R-Studio. Experiments were conducted in line with UK Home Office guidelines.

Blockade of the A2a Adenosine receptor produces partial control of tumour growth however, tumours do not completely regress (N=46 mice, 4 experiments, mean control volume 1009mm³ (686.15 ± 1332.66) versus AR-antagonist treated 712.81mm³ (445.55 ± 178.28). P = 0.008 RMANOVA, 95% CI). We therefore used flow cytometry to analyse expression of other immune checkpoints across treated and untreated tumours. Principal component analysis showed that expression of T-cell immunoglobulin and mucin-domain containing-3 (TIM3) contributed strongly to the variance between treated and control groups (P<0.0001 dimdesc correlation FactomineR). Upregulation of TIM3 therefore represents a mechanism of immune evasion in response to AR blockade. Adding anti-TIM3 mAb to AR blockade produced complete tumour regression. Risk of relapse was reduced, and double treated mice spent longer in remission when compared to AR blockade alone. (N=54 mice over 3 experiments. Mean time to relapse 41.33 (27 ± 55 days) anti-TIM3 + AR-antagonist, 13.12 (2 ± 23 days) AR-antagonist alone. Reduction in relative risk of relapse (RRR) versus control 0.5 anti-TIM3 + AR-antagonist -0.32 AR-antagonist alone. P = 0.01** Generalised Wilcoxon (95% CI, SD 19.8)). Mice without relapse were resistant to rechallenge.

Elevation of TIM3 represents a key mechanism of tumour-mediated immune evasion in response to AR blockade. Co-blockade of AR and TIM3 mediates complete tumour regression and resistance to tumour rechallenge, with no obvious adverse effects, strongly supporting the use of such dual treatment in cancer patients. This study uses large numbers to produce 80% power. Results are consistent over 3 experiments and overall response rates are high amongst mice receiving combination therapy. However, resistance to treatment evolves in 20% of mice responder mice after 40 days. Further work is required to characterise the immune memory response which protects against relapse, and the immunological events associated with acquired resistance to treatment.

C8 Dr Tariq Edward Farrah
Clinical Research Fellow / SpR in Renal Medicine
University of Edinburgh

Endothelin receptor antagonism improves lipid profiles & reduces myocardial injury in patients with chronic kidney disease

Dyslipidaemia is common in chronic kidney disease (CKD) and contributes to incident cardiovascular disease (CVD). Despite the use of statins, many CKD patients continue to have elevated lipids. Pre-clinical data suggest that endothelin-A (ETA) receptor antagonism may have beneficial effects on circulating lipids. Here, we investigated its effects on circulating lipids and markers of myocardial injury in patients with CKD.

In a fully randomised, double-blind, three-phase crossover study, 27 subjects with proteinuric, pre-dialysis CKD received 6 weeks treatment with placebo, the selective ETA receptor antagonist, sitaxentan, or long-acting nifedipine in addition to their usual medications. We excluded patients with diabetes and prior CVD. We measured circulating lipids, proprotein convertase subtilisin/kexin type 9 (PCSK9) and high sensitivity cardiac troponin I (hsTnI) at baseline and then after 3 and 6 weeks.

Eighteen (67%) subjects were prescribed a statin. Baseline lipid profiles were similar prior to each study phase (total cholesterol: 4.3 ± 0.1 mmol/L; HDL: 1.1 ± 0.1 mmol/L; LDL: 2.6 ± 0.2 mmol/L; triglycerides: 1.6 ± 0.1 mmol/L). Whereas placebo and nifedipine had no effect on lipids, 6 weeks of ETA receptor antagonism led to significant reductions in total ($-11 \pm 1\%$) and LDL ($-20 \pm 3\%$) cholesterol and triglycerides ($-20 \pm 4\%$); HDL cholesterol increased ($+14 \pm 2\%$), $p < 0.001$ vs. baseline for all. Interestingly, ETA receptor antagonism led to a $19 \pm 2\%$ fall in circulating PCSK9, $p < 0.001$ vs. baseline. Finally, hsTnI fell ($-27 \pm 19\%$) with ETA antagonism but not with placebo or nifedipine ($p = 0.01$ vs. both at week 6), effects which were independent of changes in blood pressure. There were no serious adverse events.

ETA antagonism improves lipid profiles in optimally-managed patients with CKD, effects that may occur through a reduction in circulating PCSK9. In addition, ETA antagonism led to a blood pressure-independent fall in hsTnI, a marker of myocardial injury and longer-term CVD risk. Alongside recognised reductions in blood pressure, proteinuria and arterial stiffness, ETA receptor antagonism may offer a novel strategy to reduce CVD risk in CKD. Larger, longer-term prospective studies are now needed.

C9 Mr Kevin Gallagher
Clinical Research Fellow
University of Edinburgh

Necroptosis and Ferroptosis inhibitors have significant benefit in acute ischemic kidney injury in-vivo and in-vitro.

Acute kidney injury is common. There are no pharmacological treatments for it. There is emerging evidence that programmed necrosis and linked "necro-inflammation" are crucial contributors to renal dysfunction after ischemic injury. We aimed to determine if necroptosis or ferroptosis inhibitors were beneficial in murine ischemia reperfusion injury and if evidence of necroptosis or ferroptosis could be found in human renal tubular cells in-vitro.

Mice were subjected to 18 minutes of bilateral renal ischemia followed by either 1, 2 or 28 days of reperfusion. The highly specific RIPK1 inhibitor (necroptosis inhibitor), GSK547a, or the ferroptosis inhibitor Liproxstatin-1 (Lx-1) were administered from 4 hours after the injury and compared to vehicle controls. Human proximal renal tubular cells (HK-2) underwent 3 different models of ischemia in-vitro +/- necroptosis or ferroptosis inhibitors. Multiple outputs were examined in each model.

With drug given 4 hours after injury, both GSK547a and liproxstatin-1 significantly reduced serum creatinine, TUNEL staining and tubular necrosis score compared to vehicle (24/48h)(N=9 per group). There were significant improvements in renal inflammatory and necroptotic gene expression with the two drug treatments. 28 days following renal injury, (drug given for first 2 days only) both RIPK1 inhibitor or Lx-1 treatment resulted in significantly improved glomerular filtration rate (sinistrin clearance kinetics) compared to vehicle (N=6 per group). MLKL phosphorylation (end effector of necroptosis) was found both in mouse kidney and human renal tubular cells in-vitro following ischemic injury. HK-2 cells were protected from death during ischemic injury by both drug treatments in-vitro.

We have demonstrated for the first time that specific RIPK1 inhibition and inhibition of ferroptosis in acute ischemic kidney injury can beneficially effect kidney function 1 month after injury. We have also shown for the first time that necroptosis occurs in-vitro and in-vivo in ischemic injured renal tubular cells. There may be differential effects of inhibiting necroptosis and ferroptosis on inflammation. These inhibitors are promising, novel candidates for treatment of acute kidney injury.

C10 Dr Simon Lambden
NIHR Clinical Lecturer in Intensive Care Medicine
University of Cambridge

The role of vascular endothelial Hypoxia Inducible Factor (HIF) isoforms in regulating systemic haemodynamics and vascular function in normoxic and hypoxic conditions

The vascular endothelium has important endocrine and paracrine functions, particularly in the regulation of vascular tone and immune function and has been implicated in the pathophysiology of a range of cardiovascular and inflammatory conditions. This study uses a series of murine models to explore for the first time the role of the hypoxia inducible factors, HIF1 α and HIF2 α in the vascular endothelium as potential regulators of systemic vascular function in normoxic and hypoxic conditions.

We developed a series of transgenic mouse models using the LoxP Cre recombinase system. These were the HIF1 α Tie2Cre, deficient in HIF1 α in the systemic and pulmonary vascular endothelium and the L1Cre, a pulmonary endothelium specific knockout of HIF1 α or HIF2 α . In vivo, arterial blood pressure and metabolic activity were monitored continuously. Ex vivo, femoral artery reactivity was assessed using wire myography. Analysis: in vivo: Area under the curve comparison and Mann Whitney, ex vivo: ANOVA

Under normoxia, the HIF1 α Tie2Cre mouse had increased systolic (Mean \pm (SEM) 135(2)mmHg vs 115(1)mmHg, $p=0.001$) and diastolic arterial pressure (95(1)mmHg vs 85(1)mmHg; $p<0.01$) compared to litter mate controls over the day-night cycle. VO₂ and VCO₂ were also increased (3368(58)ml/min/m² vs 2804(62) and 2933ml/min/m² vs 2458(75)ml/min/m² respectively, both $p<0.05$). Femoral arteries displayed impaired endothelial relaxation in response to acetylcholine (AUC=128 \pm 16 vs 216 \pm 17; $p<0.01$) mediated by a reduction in the NO dependent portion of the response (AUC=80 \pm 13 vs 200 \pm 11; $p<0.01$). HIF1 α L1Cre mice displayed a similar pattern (systolic arterial pressure (126(1)mmHg vs 117(1)mmHg; $p<0.005$), VO₂ (3993(98)ml/min/m² vs 3373(65)ml/min/m²; $p<0.05$), and impaired vascular relaxation.

This study shows for the first time that endothelial HIF1 α plays a constitutive role in the regulation of arterial blood pressure and vascular function. Furthermore, the pattern of increased systemic arterial pressure and impaired femoral artery dilator reactivity seen in the pulmonary endothelial specific knockouts suggests that in the vascular endothelium, HIF1 α plays has an endocrine role in regulating systemic vascular resistance.

C11 Dr Katharine Lodge
SpR Respiratory Medicine
University of Cambridge

Hypoxia induces differential protein secretion from neutrophils to drive endothelial damage in COPD

Neutrophilic inflammation characterises chronic obstructive pulmonary disease (COPD), which is also associated with hypoxia and excess cardiovascular morbidity. Release of cytotoxic proteins, e.g. neutrophil elastase (NE), can cause tissue injury although the precise mechanisms of neutrophil-mediated damage are unknown. We hypothesised that hypoxia synergises with inflammatory cytokines to promote an injurious neutrophil phenotype with enhanced capacity for local and systemic endothelial damage.

Neutrophils from exacerbating COPD patients vs age/sex-matched controls were incubated under normoxia/hypoxia. Supernatants (SN) were assayed for NE activity and/or subjected to proteomic analysis by mass spectrometry; differentially expressed proteins were validated by ELISA. α -Val360 was assayed in patient/control plasma by ELISA. Detachment/apoptosis of SN-treated human pulmonary artery endothelial cells (HPAEC) was assessed by microscopy/flow cytometry. Data were analysed by two-way ANOVA.

Hypoxia vs normoxia increased NE release ($n=6$, $p<0.0001$), with a further increase from hypoxic COPD vs control neutrophils ($n=7$, $p=0.005$). Proteomics ($n=5$) revealed differential granule protein release (up- and down-regulated) under hypoxia vs normoxia. Subsets of granule (e.g. resistin) and cytosolic (e.g. cyclophilin A) cytotoxic proteins were increased in hypoxic vs normoxic neutrophil SN, independently confirmed by ELISA, and further increased in COPD (resistin: $p=0.0337$, cyclophilin A: $p=0.0009$, $n=5$). There was no change in neutrophil apoptosis, microvesicle or extracellular trap release. Hypoxic vs normoxic neutrophil SN caused more HPAEC detachment/apoptosis ($n=4$, $p=0.0018$). An increased footprint of NE activity (α -Val360) was detected in COPD vs control plasma ($n=12$, $p=0.0048$).

Hypoxia-augmented NE release is prominent during COPD exacerbations, with increased systemic NE activity. Unbiased characterisation of the neutrophil secretome suggested a novel mechanism of selective degranulation under hypoxia. Hypoxic neutrophil SN injure endothelial cells in vitro. Hypoxia thus engenders a destructive neutrophil phenotype with enhanced release of proteins which may cause local and distant tissue damage in COPD; these novel insights may identify new therapeutic opportunities.

C12 Dr Karen Mackenzie
ECAT SCREDS Clinical Lecturer in Clinical Genetics
The University of Edinburgh

cGAS detection of micronuclei links immune surveillance to autoinflammation

Innate immune responses to self DNA are frequently implicated in autoinflammatory conditions and often generate a Type I Interferon response. Triggering of the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) has been strongly implicated in this process. Yet, how this triggering occurs was unclear given the strict compartmentalisation of self DNA within the nucleus. We aimed to use insights from monogenic autoinflammatory disease to address this fundamental question.

Murine cells deficient in the genome stability enzyme ribonuclease H2 (RNase H2) were utilised. Mutations in RNase H2 cause the autoinflammatory condition Aicardi-Goutières syndrome (AGS), and are associated with cGAS activation. GFP-cGAS was stably expressed in RNase H2 deficient cells to establish cGAS localisation. Live cell imaging, exogenous DNA damage experiments, laser microdissection and single cell transcriptomics were then conducted to determine the mechanism of cGAS activation.

Strikingly, we found that cGAS localised to structures known as micronuclei within RNase H2 deficient cells. Micronuclei are distinct from the primary nucleus and form during mis-segregation of DNA during mitosis. This finding was significant given that micronuclei are increased in the presence of genome instability and are often present during neoplastic processes. cGAS localisation to micronuclei was not restricted to RNase H2 deficiency, also occurring after exogenous DNA damage and spontaneously in human cancer cells. Live-cell imaging revealed that breakdown of the micronuclear envelope resulted in rapid accumulation of cGAS, while single cell transcriptomic analysis determined that interferon-stimulated gene expression was preferentially induced in cells containing micronuclei.

We demonstrate a novel pathway whereby micronuclei can trigger an innate immune response to self-DNA (Mackenzie KJ et al, Nature 2017;548:461). This most likely represents a cell-intrinsic immune surveillance mechanism designed to detect a range of neoplasia inducing processes. Yet, aberrant activation of this pathway could trigger autoinflammatory disease such as AGS and has wider relevance to other inflammatory conditions with a strong Type I Interferon component.

C13 Dr Andrew Owen
NIHR Clinical Lecturer in Anaesthesia and Intensive Care Medicine
University of Birmingham

Mesenchymal stromal cells reduce injury in pre-clinical post liver transplant models

End stage liver disease represents a common end point for a number of disease processes, the only current treatment for which is liver transplantation, but demand for donor organs exceeds supply. This has led to the use of more marginal donors with an increase in the rates of complications. Mesenchymal stromal cells (MSC) are a multipotent cell capable of modulating the immune system through a number of different processes and represent a potential therapy in post transplantation liver injury.

MSC were isolated using cell sorting from the bone marrow of adult C57BL/6 mice. MSC were culture expanded and tested in a bulk splenocyte reaction. Analysis of the MSC secretome following stimulation with TNF alpha and IFN gamma was undertaken using protein arrays. MSC were then infused systemically and subcutaneously in the MDR2^{-/-} and hepatic ischaemia reperfusion models of liver injury and serum and liver tissue analysed. Tracking of infused MSC was undertaken using CryoViz cryoimaging.

MSC were successfully isolated from murine bone marrow. Flow cytometric analysis of the splenocyte reaction demonstrated an ability to suppress CD8 lymphocyte proliferation. Stimulated MSC were able to secrete the anti-inflammatory cytokines IL-10 and osteoprotegerin as well as a number of adhesion molecules. MDR2^{-/-} treated with MSC systemically showed significant reductions in serum ALT and ALP, and F4/80 cells when assessed by immunohistochemistry. Flow cytometric analysis showed an increase in restorative macrophages in the treated mice. CryoViz analysis demonstrated an initial distribution to the lungs with rapid clearance over 7 days and likely redistribution to the liver after 24 hours. Mice undergoing ischaemia reperfusion injury did not see a benefit when treated with MSC.

Reducing the complications from marginal organ donation is important and may lead to an increase in the availability of transplantable organs. This pre-clinical study has demonstrated potential to reduce biliary injury similar to that seen in marginal liver transplantation using cell therapy by polarising macrophages towards a restorative phenotype. This study also demonstrates the ability of MSC to secrete IL-10 and osteoprotegerin which are able to effect macrophage polarisation.

Dr Tracie Plant

C14 ECAT Clinical Lecturer and Respiratory Registrar
University of Edinburgh

Sema3F is an autocrine neutrophil retention signal regulating neutrophil transit and effector functions during inflammation through F-actin disassembly.

Effective host responses to injury and infection require both rapid recruitment of neutrophils into tissues and timely inflammation resolution. Semaphorins are proteins that regulate motility in a variety of cell types and systems. We observed that neutrophils regulate Sema3F transcript abundance, which is expressed in the airway myeloid cell population of COPD patients. We then questioned whether Sema3F could regulate neutrophil migration and define the magnitude of the inflammatory response.

Inflammatory neutrophils express the class 3 Semaphorin, Sema3F and its obligatory co-receptor Neuropilin 2 (NRP2) and expression of both is further induced by bacterial Lipopolysaccharide (LPS). In a murine model of LPS-induced acute lung injury, we describe a phenotype where neutrophil specific knockdown of Sema3F both increases neutrophil recruitment to the airways 6 hours following LPS challenge and enhances the rate of inflammation resolution (**P=0.0079 n=9).

Conversely, intra-tracheal (IT) instillation of Sema3F in wild type mice retains neutrophils at the injury site following maximal recruitment (p=0.046, n=8). In vitro we demonstrate Sema3F reduces neutrophil chemotaxis producing "rounder cells", phagocytosis is unaffected but interestingly respiratory burst is enhanced (*P=0.0117, n=3). Myeloperoxidase activity decreases following exogenous Sema3F treatment in vitro (**p=0.0027, n=4) and vivo (*p=0.0113, n=5). We identified the location of the neutrophils in the murine lung interstitium following LPS induced lung injury. We show that intra-tracheal Sema3F holds the recruited neutrophils in the alveolar space (*P<0.0001, n=11). In vivo Sema3F induces neutrophil F-actin disassembly (**P=0.089, n=8) thus promoting neutrophil retention.

Research currently focuses on initiation and resolution as distinct phases of inflammation and neutrophil survival as a key determinant of the inflammatory response. Less focus has been placed on mechanisms retaining viable neutrophils at inflamed sites. These data suggest that Sema3F retains neutrophils acting as a migratory "brake", so that ligand and co-receptor (NRP2) could provide novel therapeutic targets for the modulation of pathological neutrophilic inflammation in respiratory disease.

Dr Christopher Rooney

C15 ST3 MM / ACF
University of Leeds / Leeds Teaching Hospital Trust

Dissemination of multiple carbapenem resistance genes in an in vitro model that simulates the human colon.

Carbapenemase producing Enterobacteriaceae (CPE) pose a major global health risk. Resistance rates have increased rapidly, with mobile genetic elements accounting for much of this increasing burden. Information on human CPE carriage and spread is largely unknown. We have used a well validated and clinically reflective in vitro model that simulates the human colon to investigate the effects of CPE and antibiotic exposure and subsequent resistance gene dissemination within the gut microbiota.

Models seeded with CPE-negative human faeces were inoculated with distinct carbapenemase (KPC, NDM) producing *Klebsiella pneumoniae* and challenged with antibiotics. Resistant populations were enumerated on selective agars (Carba-Smart, Biomerieux®/ESBL) and CPE genes within the models were confirmed by PCR assay (XCR and Check-Direct CPE Screen for BD MAX™ (CDCPE) multiplex real-time PCR assay). PacBio® long read sequencing was used to follow CPE gene dissemination between isolates of interest.

CPE populations increased during inoculation, plateauing $\approx 10 \times 5 \log_{10}$ cfu/ml in both models and persisting for the duration of the experiments (65 days). Post antibiotic administration evidence of interspecies plasmid transfer of KPC (IncFII/IncR blaKPC-2 plasmid pKpQIL-D2) & NDM (blaNDM-1, IncFIB/IncFII) genes was found. CPE populations rose from <0.01% to >45% of the Total Lactose Fermenting (TLF) populations. A single nucleotide polymorphism difference identified in a *K. pneumoniae* strain containing blaNDM-1 gene proved clonal expansion within the model. Antibiotic administration exposed undetected *K. pneumoniae* containing a blaOXA-232 on a 6141bp Col plasmid and a rise in extended spectrum beta-lactamase (ESBL) populations accounting for $\approx 69\%$ of TLF bacteria in the NDM model.

We have demonstrated that CPE exposure can lead to colonisation, clonal expansion and resistance gene transfer within healthy human gut microbiota. Furthermore, using both agar and molecular techniques we were under to detect low level colonisation. Under antibiotic selective pressure, new resistant populations were detected (ESBL and OXA232). We have proven antimicrobial stewardship is crucial to containing a CPE outbreak as misguided prescriptions will result in CPE population expansion.

C16 Dr Colin Steele
Clinical Lecturer in Colorectal Surgery
University of Glasgow

Colorectal cancer metastatic progression is determined by pro-tumourigenic neutrophil infiltrate to the metastatic niche in both mouse and human

Better understanding of the process of metastasis in colorectal cancer (CRC) will lead to development of targeted therapies that alongside surgery will improve survival. We hypothesised systemic and tissue protumourigenic neutrophils (N) promote metastases in CRC. We characterise the primary/metastatic niche in CRC and determine the influence of N on outcome. We developed an autochthonous murine model to recapitulate human disease and determine the effect of N inhibition on metastasis.

46 patients who underwent synchronous resection of colorectal primary and liver metastases between April 2002 and June 2010 at Glasgow Royal Infirmary were included in this retrospective study. Ethical approval and to access patient tissue was authorised by the NHS GGC biorepository #357. Assessment of the effect of N burden and outcome was analysed using Kaplan Meier curves and Cox regression analysis. Villin-Cre-ER; KrasG12D/+, p53fl/fl, N1icdf/fl mice were generated in house.

Blood neutrophil counts, MPO/CXCR2 staining for N, CD68 for macrophages, CD4/8 for T cells was performed in primary and metastatic CRC. Elevated blood N count ($P=0.021$) and N burden of metastases ($P<0.05$) was associated with poor outcome following resection of CRC and metastases. Blood N count correlated strongly with metastatic N burden but not primary CRC N burden (Spearman's $P<0.05$). Metastatic N burden was the main determinant of prognosis on multivariate analysis (Cox regression $P<0.05$). Villin-Cre-ER; KrasG12D/+, p53fl/fl, N1icdf/fl mice showed significant numbers of CXCR2+ N in the metastatic niche via Notch induction of CXCL5. Inhibition of N using Ly6G antibody or CXCR2 small molecule led to reduction of metastatic burden in these mice through an effect on systemic N numbers.

CXCR2 positive neutrophils promote metastatic progression in mice and can be inhibited improving metastatic burden. Analysis of synchronously resected human CRC/liver metastases suggests systemic levels of N and N infiltrate to metastases conveys poor prognosis and promotes disease recurrence. No such influence of N at the primary site exists. CXCR2 positive neutrophils may represent a target for therapy in metastatic CRC, through better understanding their role in the metastatic niche.

C17 Dr Olivia Swann
Paediatric Trainee and ECAT Wellcome Trust Clinical Fellow
Centre for Immunity, Infection and Evolution, Institute of Immunology and Infection Research, University of Edinburgh, Edinburgh

Two complement receptor one alleles have opposing associations with cerebral malaria and interact with α +thalassaemia

Malaria has been a major driving force in the evolution of the human genome. In sub-Saharan African populations, two neighbouring polymorphisms in the Complement Receptor 1 (CR1) gene, named SI2 and McCb, occur at high frequencies, consistent with selection by malaria. However, previous epidemiological studies have been contradictory. This study investigated the relationship between these variants and severe malaria as part of a large case control study in Kenya.

Cases were children <14 years with a diagnosis of severe malaria presenting to the Kilifi District Hospital, Kenya and controls were children born consecutively within the study area. Samples were genotyped using Sequenom MassARRAY®. Analysis used mixed effects logistic regression with adjustment for ethnicity, location, sickle cell trait, ABO blood group and α +thalassaemia genotype. Optimal model fit was determined using Akaike information criterion.

1716 severe malaria cases and 3829 controls were available for analysis. Opposing associations were noted for the two CR1 polymorphisms. The SI2 allele was significantly associated with protection against all cases of severe malaria (adjusted OR 0.78, 95% CI 0.64 - 0.95, $p = 0.011$), but specifically against cerebral malaria (CM, aOR 0.67, 95% CI 0.52 - 0.87, $p = 0.006$) and death (aOR 0.50, 95% CI 0.30 - 0.80, $p = 0.002$). In contrast, the McCb allele was associated with increased odds of CM (aOR 1.19, 95% CI 1.02 - 1.38, $p = 0.025$). Unexpectedly, a novel interaction between SI2 and α +thalassaemia genotype was identified, such that the protective associations of SI2 were only seen in individuals of normal α -globin genotype.

The protective association between SI2 and both CM and death imply evolutionary selection by malaria, whereas the increase in odds of CM with McCb suggests selection pressure from another disease. Laboratory work is underway to establish the function of these variants. The novel interaction between SI2 and α +thalassaemia may have obscured the association in other studies. This work reminds us that no gene acts alone and that apparently conflicting studies may conceal important information.

Poster Competition - Group D

Dr Johnathan Cooper-Knock

D1

NIHR Clinical Lecturer

University of Sheffield / Sheffield Teaching Hospitals

Targeted genetic screen of RNA-binding proteins in amyotrophic lateral sclerosis reveals novel genetic variants with synergistic effect on clinical phenotype

Amyotrophic lateral sclerosis (ALS) is underpinned by a polygenic rare variant architecture. Identified genetic variants of ALS include RNA-binding proteins containing prion-like domains (PrLD). We hypothesised that screening related proteins will yield novel genetic variants of ALS. 10% of ALS patients carry G4C2-repeat expansion of C9orf72. G4C2-repeat RNA sequesters RNA-binding proteins suggesting that loss-of-function mutations in G4C2-binding partners contribute to ALS pathogenesis.

Genomic DNA was extracted from 109 ALS patients including 15 C9orf72-ALS patients. DNA was enriched for selected RNA-binding proteins and known genetic variants of ALS using a custom design Agilent SureSelect Target Enrichment kit. Sequencing was performed using an Illumina HiScan platform. Rare deleterious mutations were defined by frequency with ExAC of $<1/10000$ controls, and a Phred-scaled CADD score >10 (top 10% most deleterious). We validated changes with low read depth by Sanger sequencing.

We identified 42 patients with a rare deleterious mutation of which 6 patients carried more than one mutation. We identified new mutations in twelve known ALS genes which served as a validation of our strategy. We identified 19 patients with at least one mutation in a RNA-binding protein containing a PrLD. The number of mutations per patient correlated with rate of disease progression (t-test, $p=0.0033$). We identified 18 patients with a single mutation in a G4C2-repeat binding protein. Five patients also carried a G4C2-repeat expansion in C9orf72. Patients with a G4C2-binding protein mutation in combination with a C9orf72 expansion had a significantly faster disease course (t-test, $p=0.025$).

Our data is consistent with a polygenic model of ALS in which multiple rare variants act collectively to cause disease. We provide evidence for a number of entirely novel genetic variants of ALS caused by mutations in RNA-binding proteins. Moreover we show that these mutations act synergistically with each other and with C9orf72 expansions to modify the clinical phenotype of ALS. This work has significant implications for ALS therapy development.

Dr Nicholas Evans

D2

Clinical Lecturer

University of Cambridge & Addenbrooke's Hospital

Inflammation in Atherosclerosis is Associated with Disease Severity in Acute and Chronic Cerebrovascular Disease - A Prospective Multimodal Imaging Cohort Study

Inflammation in atherosclerosis contributes not only to plaque vulnerability, but also correlates with concentrations of circulating matrix metalloproteinases (MMPs). In turn, MMPs are implicated in blood-brain barrier disruption, contributing to the development of chronic cerebral small vessel disease (SVD) and larger acute infarct volumes. This study investigated directly the association between carotid atherosclerotic inflammation and both acute and chronic cerebrovascular disease in vivo.

In this single-centre cohort study, adults with ischaemic stroke and ipsilateral carotid artery stenosis $>50\%$ underwent acute assessment of plaque inflammation using fluorodeoxyglucose (FDG)-positron emission tomography. Serum high-sensitivity C-reactive protein (hsCRP) was measured concurrently. SVD severity (Fazekas scale) and infarct volumes were assessed by 3-Tesla MRI at baseline and 90 days. Participants provided written consent. Nottingham 1 Research Ethics Committee approved the study.

Of 26 participants, 15 (57.7%) had no/mild and 11 (42.3%) had moderate/severe SVD. Adjusting for cardiovascular risk factors, carotid FDG uptake (maximum tissue-to-background ratio, TBRmax) was independently associated with more severe SVD (OR 6.18, 95% CI 2.1-18.2, $p=0.004$). Carotid TBRmax was also strongly independently associated with interval change in infarct volume at 90 days (coefficient=0.81, $p=0.002$). There was no association between TBRmax and degree of carotid artery stenosis ($p=0.91$ for trend). Furthermore, inflammation was a diffuse process along the artery on spatial analysis of FDG uptake. TBRmax of the most diseased segment of the symptomatic carotid artery had a moderate correlation with hsCRP concentration ($rs=0.53$, $p=0.01$). There were no adverse events.

Inflammation within carotid atherosclerosis is associated with more severe SVD, an important cause of dementia, and with adverse evolution of the acute infarct in the early post-stroke setting, a prognostic marker for poor clinical recovery. Our study has a number of strengths, in particular the multimodal approach to measuring pathology in vivo at an early stage following the acute stroke. The study is limited by its small sample size, and validation in a larger sample is necessary.

Dr Jenna Gregory

D3 ECAT SCREDS Clinical Lecturer and Honorary StR in Histopathology
University of Edinburgh

Probing the Spatial Transcriptome of Motor Neurone Disease

The pathological mechanisms underlying the selective degeneration of motor neurones in motor neurone disease (MND) are poorly understood. The dysregulation and pathological accumulation of RNA-binding proteins is a common neuropathological finding in the majority of cases of MND. As such, there is much interest in assessing RNA metabolism and transcriptional dysregulation in MND post-mortem tissue. However, previous studies have often been limited by lack of spatial resolution.

This study presents the first description of a technology called spatial transcriptomics (ST) to assess spatial RNA sequencing in human post-mortem neural tissue. Using this technology, we were able to analyse the transcriptome, with spatial resolution, of post-mortem brain tissue from patients with MND.

ST analysis revealed sixteen dysregulated RNA transcripts in six disease-related pathways: (i) proteostasis, (ii) RNA/DNA-binding proteins, (iii) mitochondrial metabolism, (iv) extracellular matrix, (v) excitotoxicity and (vi) apoptosis. Notably, identifying two spatially dysregulated transcripts: (i) GRM3 and (ii) USP47, whose spatial dysregulation could account for regional susceptibilities to the disease process in MND. Crucially, these transcripts represent potential drug targets. Previously, GRM3 agonists have been trialled in schizophrenia and deubiquitinating proteins, such as USP47, have been a longstanding drug target in the oncology field.

Taken together these findings reveal transcriptional dysregulation of key genes in the pathogenesis of MND and shed light on the selective vulnerabilities of (i) brain regions and (ii) specific cell types, to the disease process in MND, highlighting potential therapeutic targets.

Dr Christopher Holland

D4 Foundation Year 1 Doctor (Academic)
Newcastle University / The James Cook University Hospital

A direct quantitative comparison of PETMR to PETCT for brain scans of patients with dementia

PETMR (Positron Emission Tomography Magnetic Resonance) is a recent innovation in hybrid imaging. Compared to PETCT (PET Computed Tomography) advantages of PETMR include reduced radiation exposure & superior soft tissue contrast, but implementation challenges include correct PET attenuation correction (AC). FDG PET brain images from dementia patients obtained with PETMR and PETCT were quantitatively compared, with a hypothesis that PETMR could be substituted for PETCT.

Patients referred for brain FDG PETCT following dementia diagnostic pathways were invited to undergo PETMR scanning following routine PETCT. Participants gave informed verbal consent. No additional FDG was given. 7 sequential datasets were acquired. Measured FDG uptake in PETCT and PETMR was compared region-wise through a fully automated protocol. Results were analysed using Bland-Altman analysis. This was a service evaluation at Newcastle PET centre, not research as per the HRA definition.

7 patients underwent sequential PETCT and PETMR scans (interval 18-46 minutes). Images were automatically processed with registration of CT-based images onto MR-based images and segmentation of brain and bone from MR and CT respectively. Mean percentage differences over whole brain and subregions (overall and as a function of distance from bone) between the PETCT and PETMR images (with decay correction) were calculated. Preliminary analysis indicates PETMR values systematically higher than PETCT (mean diff 13.2% std dev 10.7%), Bland-Altman analysis showing reasonable general agreement between brain regions within each patient (average std dev 5.9%). A different relationship between PETMR and PETCT values arises within 5-10mm of bone consistent with errors in MR bone characterisation.

Relative to previous comparisons evaluating only differences in AC methods there is larger variation between brain regions (std dev 5.9% vs 2.0%). Possible explanations for this and the higher PETMR than PETCT values include scan interval, registration and PET technology, with further investigation required and analysis ongoing. Need for improvement in MR bone characterisation is also indicated. This is a small sample size only applying to brain scans in dementia and this specific PETMR scanner.

D5 Mr Aimun Jamjoom
Neurosurgery Registrar
University of Edinburgh

Large-scale single-synapse resolution analyses of synaptopathy following traumatic brain injury

Traumatic brain injury (TBI) is a major cause of cognitive impairment with significant economic and social implications. The fundamental molecular and cellular mechanisms of TBI are poorly understood. We examined the molecular composition and anatomical distribution of individual excitatory synapses in a mouse model of TBI using a novel imaging approach called 'Synaptome mapping' which permits single synapse quantification across the whole mouse brain.

Genetically modified mice expressing fluorescent-labelled postsynaptic proteins PSD95 and SAP102 (n=44) were randomised to a fluid percussion injury or control at 7 and 28 days. Brain tissue sections were imaged using confocal microscopy. Synapse puncta density, size and intensity from 222 brain regions were analysed using machine learning algorithms. Axonal (amyloid precursor protein-APP), microglial (Iba-1) and presynaptic bouton (SV2A) markers were assessed with immunohistochemical methods.

At 7 days, despite evidence of increased APP aggregates in the corpus callosum of the injury mice (p=0.002), there was no difference in synaptic metrics between the cohorts. By 28 days, we observed a reduction in synaptic puncta density distal to the injury site, particularly the hippocampus coupled to an increase in microglia (Iba-1) count (p=0.03). PSD95 and SAP102 density changes had a strong positive correlation (r=0.8; p<0.0001). We also observed evidence of synapse recovery in the cortex between 7 and 28 days. SV2A (presynaptic marker) had a positive correlation with PSD95 puncta density (r=0.8; p<0.01) and a negative correlation with PSD95 puncta area (-0.6; p=0.02). Microglia count was negatively correlated (r=-0.6; p<0.001) with synapse density.

Focal traumatic injury induced progressive region-specific loss of synapses for which microglia may play a role. Hippocampal synapses demonstrated vulnerability to traumatic insult which may contribute to post-TBI cognitive dysfunction. Our study highlights the value of brain-wide synaptome mapping technology and suggests a capacity for synaptic recovery which could be a therapeutic target.

D6 Dr Zoeb Jiwaji
PhD Training Fellow / Honorary Registrar in Anaesthesia and ICM
University of Edinburgh

Neuron-astrocyte signalling alters transcription to control CNS homeostasis and is dysregulated by ageing and anaesthesia.

Synaptic activity alters transcription in neurons to drive cellular and circuit-level changes necessary for memory and neuronal health. However, the consequences of synaptic activity on non-neuronal cells are poorly understood. Astrocytes (one of the most common CNS cell types) have key roles in CNS homeostasis and metabolism. We investigated if synaptic activity regulates astrocyte transcription and function, and whether these pathways are altered by ageing or when neuronal activity is suppressed during anaesthesia.

Activity in a neuron-astrocyte co-culture system was pharmacologically manipulated for 24 h, and astrocyte transcription measured using RNA-sequencing. Transcriptional changes were confirmed in vivo using astrocyte-specific GFP-ribosome reporter mice exposed to a light-stimulus paradigm (24 h of light vs dark) to achieve high vs low activity in the visual cortex. Activity-regulated gene expression was compared in adult (4 month) vs aged (2 y old) mice, and mice undergoing 6 h anaesthesia.

Synaptic activity alters a wide programme of astrocyte gene expression, with 505 genes changed >1.3 fold in high vs low activity conditions (adjusted p<0.05). Transcriptional changes correlated well between in vitro vs in vivo paradigms, and astrocyte activity-regulated gene expression was impaired by both ageing and anaesthesia. Astrocyte metabolic genes constituted the largest upregulated family. Using intracellular optical metabolic nanosensors, we confirmed that synaptic activity enhances astrocyte metabolic flux, and determined that activity-dependent signalling occurs via the cAMP response element binding-protein (CREB) pathway. CREB inhibition reversed activity-induced effects, and CREB activators were sufficient to boost astrocyte metabolism in low-activity conditions.

We have determined that synaptic activity alters astrocyte transcription to control astrocyte metabolic flux, offering insight into a novel pathway by which neurons tune astrocyte function to regulate brain homeostasis. These signals are dysregulated by both ageing and anaesthesia, and may increase brain vulnerability during the perioperative period. Finally, we have identified the astrocyte CREB pathway as a putative drug target to enhance CNS resilience signals in vulnerable patients.

Secular trends in adult epilepsy-related mortality: a nationwide retrospective cohort and case-control study using validated routine administrative data

This ongoing study is the first national study identifying the burden of adult epilepsy-related mortality in Scotland, necessary as epilepsy is common and likely associated with an increased risk of early death. Hypotheses: 1) Rate and comparative risk of epilepsy-related mortality are higher than the national average; 2) a substantial proportion of epilepsy-related deaths are avoidable; 3) sociodemographic/clinical characteristics differ between surviving and deceased adults with epilepsy.

Design: a Scotland-wide, retrospective cohort and case-control study identifying deaths occurring between 01/01/09-16 from validated administrative primary and secondary care data linked to death certificates & prescription data. Participants: deceased adults (age \geq 16 years) with epilepsy. Controls are 1:1 age-/sex-matched live controls being recruited from South East Scotland. Analysis: identifies mortality rate (MR) & standardised mortality ratio (SMR) (95% CI). Ethics: REC15/SS/0165

2,149 epilepsy-related deaths were identified. Age-standardised MR was 6.8 (CI 6.0-7.6)/100,000 in 2009, 6.4 (CI 5.6-7.1)/100,000 in 2012, and 9.1 (CI 8.2-9.9)/100,000 in 2015. Deaths were significantly more common in young adults (aged \leq 44 years); SMR for ages 16-24 years was 6.0 (CI 2.3-9.7), and for ages 25-34 years it was 3.7 (CI 1.9-5.6). Sudden unexpected death in epilepsy (SUDEP) accounted for 38% of epilepsy-related deaths at age \leq 44 years. 60% of SUDEP cases were from Scotland's most deprived areas (Index of Multiple Deprivation Quintiles 1-2). Avoidable mortality was estimated at 49% (235 case notes reviewed). Preventable risk factors included failure to refer to specialist epilepsy services, lack of patient/carer education, drug errors, and delayed specialist review.

Despite available advances in diagnosis and treatment for epilepsy, premature epilepsy-related mortality in adults remains common and is not reducing in rate. Those aged \leq 44 years are at particular risk and those in transition between child and adult healthcare services are at the highest risk. A substantial proportion of epilepsy-related deaths may be preventable. Strengths: population-based study using validated diagnostic codes. Limits: assigning causality in an observational study.

D8**Dr Yi Shiau Ng**

NIHR Clinical Lecturer in Neurology

Wellcome Centre for Mitochondrial Research, Newcastle University, UK & Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

An Observational Cohort Study of Cardiac manifestations in Adult Patients with Mitochondrial Disease Arising from Nuclear Gene Mutations

Primary mitochondrial diseases are one of the most common groups of genetic disorders with an estimated prevalence of 1 in 4300. Mutations in the mitochondrial DNA and nuclear genome can cause mitochondrial dysfunction and defects in the oxidative phosphorylation, leading to the development of the mitochondrial disease. Cardiac involvement in mitochondrial diseases may present as a prominent clinical manifestation, albeit most frequently as part of a wider multi-system phenotype. Whilst cardiac surveillance is routinely advocated in clinical practice, there is limited data on the prevalence of cardiac disease, specifically in adults with mitochondrial disease caused by mutations in the nuclear genome. Aims: To comprehensively assess the spectrum of cardiac abnormality in patients with confirmed mitochondrial disease due to nuclear gene mutations and devise genotype-specific cardiac surveillance recommendations.

Adult patients who harboured nuclear gene mutations were identified from the Mitochondrial Disease Patient Cohort (REC ref 13/NE/0326), a national cohort study of mitochondrial disorders in the UK. These patients were followed up regularly by the NHS Highly Specialised Service for Rare Mitochondrial Disorders in Newcastle every 6-24 months between 2007 and 2017. Newcastle Mitochondrial Disease Adult Scale (NMDAS), case notes and cardiac investigations including serial ECGs and echocardiograms were analysed. Significant cardiac involvement related to the mitochondrial dysfunction was defined based on the NMDAS as follows: high-grade atrioventricular block (Mobitz type 2, 2nd degree or 3rd degree), ventricular pre-excitation, documented symptomatic arrhythmias, impaired left ventricular (LV) function, and concentric left ventricular hypertrophy (LVH).

We identified 161 adult patients of which 86% (n=136) had a complete data set suitable for analysis (mean age 51.8 years, 95% CI 51.5 – 52.0, range: 18-85 years; female 65%) with 11 nuclear gene mutations (TWNK n=45, POLG n=29, RRM2B n=24, OPA1 n=24, GFER n=3, YARS2 n=2, TYMP n=2, ETFDH n=2, SDHA n=2, TRIT1 n=2 and AGK n=1). The median follow up duration was eight years. The predominant clinical features associated with the mitochondrial disease were ptosis (66%), chronic progressive external ophthalmoplegia (62%), myopathy (45%) and cerebellar ataxia (44%). Seventeen significant cardiac abnormalities were identified in fourteen patients (9%): LVH (n=6), isolated impaired LV function (n=6), left bundle branch block (n=2), cardiomyopathy which required transplantation (n=1), chronic atrial fibrillation (n=1) and ventricular tachycardia secondary to myocardial infarction (n=1). Nuclear gene mutations associated with an early-onset (<30 years old) LVH and cardiomyopathy were YARS2, AGK and GFER. Coronary artery disease was identified in three patients. Overall, the frequencies of cardiovascular risk factors were as follows: hypertension (24%), diabetes mellitus (12%), hypercholesterolemia (22%) and obesity (BMI>30) (32%).

We present the findings of the most extensive observational study of cardiac abnormality in mitochondrial disease secondary to nuclear gene defects to date. We show that the majority of adult patients do not have cardiac manifestation, and that cardiac involvement is genotype specific in mitochondrial disease due to nuclear gene mutations. It may be clinically sufficient and more cost-effective to limit cardiac surveillance to patients with specific 'high risk' mutations. Coronary artery disease is more likely to be related to the underlying cardiovascular risk factors than the mitochondrial dysfunction in adult

D9 Dr Ariel Ong
Academic Foundation Doctor
NHS Lothian

Long-term mortality and recurrent vascular events in lacunar versus non-lacunar ischaemic stroke

Lacunar stroke has traditionally been considered a more benign type of stroke. However, relatively little is known about the very long-term prognosis of lacunar versus other types of ischaemic stroke. We investigated the long-term risks of mortality and recurrent vascular events among people with lacunar compared with non-lacunar ischaemic stroke.

We included participants from a prospective hospital-based cohort study, which recruited participants between 2002 and 2005. We followed participants using multiple hot pursuit methods and, in the longer term, by linkage to hospital admission and mortality records. Using Kaplan-Meier survival analyses, we obtained cumulative incidence of mortality, recurrent stroke and myocardial infarction (MI) for lacunar and non-lacunar groups. We compared risk of events using Cox regression modelling to obtain unadjusted and adjusted hazard ratios (HRs) for mortality and sub-hazard ratios (accounting for competing risks) for cardiac death, recurrent stroke and MI. We obtained effect estimates for the entire time period, 0-1 year and 1-year onwards.

We included 812 people (283 lacunar) with first-ever ischaemic stroke. During maximum 14 years follow-up (median 9.2 years), there were 519 deaths, 181 recurrent strokes, and 74 MIs. Mortality risk was lower in lacunar versus non-lacunar stroke (adjusted HR 0.79, 95% CI 0.65-0.95), but this difference attenuated from one-year post-stroke onwards. There was no clear difference in risk of recurrent stroke (adjusted SHR, 0.93, 95% CI 0.67-1.26) or MI (adjusted SHR 1.02, 95% CI 0.62-1.68) for the entire follow-up period, with similar findings obtained at 1-year post-stroke and 1-year onwards.

In the long-term, all-cause mortality risk is slightly lower in patients with lacunar compared to non-lacunar stroke, but there is no difference in the risk of recurrent stroke or MI. Secondary prevention of vascular events is equally important in people with lacunar as compared with other types of ischaemic stroke.

D10 Dr Benjamin Perry
Academic Clinical Fellow, ST3 Psychiatry
University of Warwick / Coventry and Warwickshire Partnership NHS Trust

Dysglycaemia, inflammation and psychosis: Cross-sectional and longitudinal analysis from the UK ALSPAC birth cohort

Psychosis is associated with both dysglycaemia and low-grade inflammation, which may represent a distinct pathophysiological subtype of psychosis. Population-based studies investigating the interplay between these factors are scarce. We aimed to (1) explore the direction of association between markers of dysglycaemia, inflammation and psychotic experiences (PEs); and (2) explore whether dysglycaemia moderates and/or mediates the association between inflammation and PEs.

Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort were modelled using logistic and linear regression to examine cross-sectional and longitudinal associations between markers of dysglycaemia (age 9 & 18), IL-6 (age 9), and PEs (age 12 & 18). We tested for an interaction between dysglycaemia and IL-6 on risk of PEs at age 18, and tested whether dysglycaemia mediated the relationship between IL-6 and PEs.

Based on 2627 participants, at age 18, insulin resistance (IR) was associated with PEs (adjusted OR=2.32; 95% CI, 1.37-3.97). IR was associated with IL-6 both cross-sectionally and longitudinally. Interaction analyses under a multiplicative model showed that IR moderated the association between IL-6 at age 9 and PEs at age 18 (adjusted OR for interaction term=2.18; 95% C.I., 1.06-4.49). Mediation analysis did not support a model of IR mediating the relationship between IL-6 and PEs.

IR is associated with PEs in young people even before the onset of clinical psychosis. Metabolic alterations may interact with childhood inflammation to increase risk of PEs. The findings have implications for clinical practice and future research.

D11**Dr Elaine Rutherford**

Clinical Lecturer

University of Glasgow and Renal and Transplant Unit, Queen Elizabeth University Hospital, Glasgow

The effect of allopurinol on left ventricular mass index - a randomised controlled trial

Premature cardiovascular death is a leading cause of death amongst patients on dialysis. Increased left ventricular mass index (LVMI) is strongly associated with all cause and cardiovascular mortality. Allopurinol has been shown to reduce LVMI in randomised trials in chronic kidney disease, diabetes and ischaemic heart disease. We investigated whether allopurinol might also regress LVMI in a haemodialysis population by conducting a multicentre double blind randomised controlled trial.

Full regulatory and ethical approvals were obtained (EoS0051). 80 haemodialysis patients consented to this double blinded study and were randomly assigned to allopurinol 300mg or placebo after each dialysis session for 1 year. Block randomisation was used to determine treatment allocation. LVMI was assessed by cardiac magnetic resonance imaging performed on the post HD day at baseline and after a year of treatment. A t test was used to determine between groups differences in change in LVMI.

Participants on placebo and allopurinol were well matched, pre-HD diastolic BP was lower in the allopurinol group. 53 patients completed the study and were included in the final analysis, by intention to treat, one participant (on allopurinol) was excluded from analysis prior to unblinding because of a protocol breach. A reduction in urate was achieved with allopurinol: change in urate ($\mu\text{mol/L}$) placebo $+21 \pm 100$, allopurinol -44 ± 84 , $p=0.01$. In an unadjusted analysis allopurinol did not regress LVMI - change in LVMI (g/m^2): placebo $+3.6 \pm 10.4$, allopurinol $+1.6 \pm 11$ $p=0.49$. In a sub-group analysis of those patients who achieved a reduction in urate of 20% or more with allopurinol, allopurinol significantly reduced LVMI- change in LVMI placebo $+3.6 \pm 10.4$ versus -2.9 ± 7 $p=0.03$.

Compared with placebo, treatment with allopurinol did not regress LVMI in haemodialysis patients over a year of therapy. However, in those patients on allopurinol who achieved a 20% reduction in urate there was a significant reduction in LVMI suggesting effect of allopurinol on LVMI is dependent on an effective dose. A large scale trial of the effect of allopurinol on cardiovascular outcomes is warranted, with the dose in the active arm titrated to achieve a reduction in urate of at least 20%.

D12**Dr Esther Sammler**

Consultant Neurologist and Honorary Senior Clinical Lecturer

University of Dundee / MRC Protein Phosphorylation and Ubiquitylation Unit

Biomarkers in Parkinson's disease

There is compelling evidence for the role of the leucine-rich repeat kinase 2 (LRRK2) and in particular its kinase function in Parkinson's disease (PD). LRRK2 phosphorylates a subgroup of RAB proteins. We have developed a facile and robust assay to quantify LRRK2 kinase pathway activity in human peripheral blood. This allows patient stratification based on LRRK2 kinase activity and identify individuals who might benefit from LRRK2 kinase inhibitor treatment that are now in clinical trials.

Human peripheral blood neutrophils and monocytes were isolated by immunonegative selection and treated with and without the specific LRRK2 kinase inhibitor MLI-2. Cells were lysed and subjected to quantitative immunoblotting for total and phosphorylated LRRK2, Rab10 and controls. Participants from 2 centers included 14 with LRRK2-associated PD, 3 with VPS35-associated PD, 12 non-manifesting LRRK2 mutation carriers, 28 idiopathic PD (iPD) patients and 30 controls. Ethical approval was in place.

LRRK2 kinase pathway activity as measured by LRRK2 controlled Rab 10 phosphorylation is significantly elevated in peripheral blood neutrophils from 2 patients and 3 non-manifesting carriers (NMC) of the LRRK2 [R1441G] mutation compared to 19 iPD and 21 controls. No significant difference was seen in 12 patients and 9 NMC of LRRK2 [G2019S]. Furthermore, a highly significant effect on LRRK2 controlled Rab10 was demonstrated in neutrophils and monocytes of 3 patients with VPS35[D620N] associated PD compared to 9 cases with iPD and 9 controls. In all samples, MLI-2 treatment suppressed Rab10 phosphorylation to background levels confirming that Rab10 phosphorylation was mediated by LRRK2. Data were analysed by one-way ANOVA with Tukey multiple comparison test (means \pm SD; * $P < 0.0001$).

Our LRRK2 controlled Rab phosphorylation assay in human peripheral blood offers the prospect of identifying individuals with increased LRRK2 kinase activity. Significantly increased LRRK2 activity is demonstrated in individuals with the LRRK2 [R1441G] mutation, but also with VPS35 [D620N], another PD associated gene product. The latter suggests that VPS35 [D620N] causes PD via hyperactivation of LRRK2 and that patients with this mutation may also benefit from LRRK2 kinase inhibitor treatment.

D13

Dr Matilde Sassani
PhD student
University of Sheffield

Investigating bioenergetic dysfunction in motor neurone disease using 31 phosphorus magnetic resonance spectroscopy: a feasibility study

Motor neurone disease (MND) is a fatal neurodegenerative condition likely characterised by deficits in adenosine triphosphate (ATP) and phosphocreatine (PCr). Phosphorus magnetic resonance spectroscopy (31P-MRS) allows in vivo detection of ATP and PCr. Although a few previous muscle studies exist, no 31P-MRS brain study has yet been conducted in MND. The objective of this pilot study is to demonstrate feasibility of a 31P-MRS protocol to study bioenergetics in both brain and muscle in MND.

31P-MRS spectra were acquired from 12 healthy volunteers. Signal to noise ratios, coefficients of repeatability (CR), coefficients of variability (CV), Bland-Altman upper and lower limits of agreement (ULO, LLO), and measurement bias were calculated. In muscle, a dynamic protocol to measure changes in PCr during muscle contraction was tested in four healthy volunteers. Pilot brain and muscle 31P-MRS spectra have been acquired employing the developed protocol from four MND patients, to date.

In healthy volunteers, signal to noise ratios for brain PCr and γ ATP were 138.0 (\pm 30.9) and 37.9 (\pm 7.8), respectively; deep white matter PCr/ γ ATP was 1.11 (\pm 0.07) and was characterised by CR=0.34, CV=6.1%, ULO=0.31, and LLO= -0.31. No systematic bias was detected. Mean muscle PCr/total phosphorus signal was 0.51 (\pm 0.02) at rest and 0.41 (\pm 0.02) at the end of muscle contraction in healthy volunteers. In patients, deep white matter PCr/ γ ATP was 1.30 (\pm 0.07) and mean muscle PCr/total phosphorus signal results were 0.45 (\pm 0.16) at rest and 0.18 (\pm 0.11) following exercise. Spectra acquisition was well tolerated by healthy participants and MND patients in all cases.

We have demonstrated feasibility of applying 31P-MRS in healthy participants and MND patients. The technique yields good quality spectra, is repeatable and reproducible, and was well tolerated by participants even in the presence of significant disability. The technique has potential to identify patients with abnormal bioenergetics, decipher mechanisms underpinning energy dysmetabolism, and merits further investigation as a biomarker for future clinical trials.

D14

Dr Zhangjie Su
Junior Specialist Doctor
The National Hospital for Neurology and Neurosurgery

Craniocervical abnormalities in the hypermobility spectrum of Ehlers-Danlos Syndrome (EDS) detected by kinematic MRI: A comparative cohort study

EDS is a hereditary connective tissue disorder leading to hypemobile joints including the craniocervical junction (CCJ). Resulting CCJ instability may lead to neurologic manifestation and serious complications. Diagnostic imaging is required to determine management and surgery plans. CCJ abnormalities may have a dynamic element and not be captured in recumbent MRI. We aim to evaluate the craniocervical abnormalities in EDS patients using kinematic MRI since there is no such evidence available.

28 EDS patients and 28 control subjects (non-EDS with cervical spondylosis) underwent kinematic MRI of cervical spine in its neutral, flexion and extension positions. Global and segmental movement parameters of CCJ and cervical spine were measured from T2 images in the midline sagittal plane. These parameters included the clivo-axial angle, Grabb-Oakes line, cervical lordosis, and the range of movement (ROM) of cervical spine from flexion to extension, which were compared between the 2 groups. The clivo-axial angle in neutral position was 139.7 \pm 10.4 degrees in the EDS group compared with 148.9 \pm 8.4 degrees in the control group (p <0.01). No significant differences in clivo-axial angles were found in flexion or extension between the 2 groups. Measures of the Grabb-Oakes line revealed no difference between the 2 cohorts.

The cervical ROM (between flexion and extension) was 74.6 \pm 24.4 degrees in EDS patients vs. 39.4 \pm 11.3 degrees in the controls (p <0.0001). Cervical ROM from neutral to flexion was 25.4 \pm 11.3 degrees in EDS and 14.0 \pm 9.6 degrees in the controls (p =0.019), and the ROM from neutral to extension was 51.5 \pm 25.4 degrees in EDS and 22.4 \pm 12.2 degrees in the controls (p =0.002). No significant difference in cervical lordosis was found between the 2 cohorts in neutral position. EDS patients with neck symptoms exhibited a more acute clivo-axial angle in neutral position and wider ROM in the cervical spine compared to non-EDS patients with cervical spondylosis. This static craniocervical feature and dynamic cervical spine instability may contribute to their clinical manifestation. Our study sheds light on the pathophysiology of EDS and is the first to show the potential of kinematic MRI in detecting craniocervical junction abnormalities in the EDS hypermobility spectrum.

D15

Dr Akila Visvanathan

Clinical Academic Fellow

University of Edinburgh / NHS Lothian

A qualitative study to improve communication and shared decision making on treatments after acute severe stroke

Informed decision-making on treatments after a severe stroke is challenging: prognosis is uncertain, patients may not have capacity to participate and relatives may not know what the patients' wishes are.

However, this is important as many treatments e.g. tube feeding after a stroke increases survival with disability, rather than to independent living. Our aim was to explore the decision-making process with patients and relatives in order to provide insight to clinicians to tailor discussions.

After ethical approval, 15 patients with a moderate to severe stroke and 24 relatives participated in semi-structured interviews in this longitudinal qualitative study. We explored how they made treatment decisions and what was important for them to do so. We obtained feedback on tools that could aid communication. Participants were followed up at 6 months when we explored their subsequent feelings about the decisions made. An inductive approach was adopted and data were analysed thematically.

Patients did not think they had any treatment decisions to make. Most took any treatments in the hope of regaining independence. Positive information was important. At 6 months, surviving patients were hoping for further recovery and support. Most relatives did not initiate active treatment based on the patients' pre-stroke health. A third did due to lack of knowledge of patient preferences but eventually withdrew treatment after discussion of prognosis and patients' likely wishes. Viewing brain scans and using visual aids to complement verbal communication was appealing to many. All relatives reported that the patient would not value survival with severe disability and at 6 months, were accepting of the outcome of death or disability and treatment decisions that were made at the time.

Patients and relatives may have different goals and views. Clinicians need to be aware of this when discussing treatments with relatives. Information needs to be tailored to the individual and an attempt to involve patients in making decisions. A standardised tool could be helpful in this situation. Although limited to a small selected population, this is the first longitudinal qualitative study exploring decision-making after severe stroke. On-going work in this area will inform future steps.

#MedSciLife

#MedSciLife is a campaign created by the Academy of Medical Sciences to share the life experiences of those working in biomedical and health research, to celebrate diversity and provide advice and support to medical researchers at all stages of their career.

Our aim is to create opportunities for researchers at all levels to share the different ways they work, allowing them to pass on advice and practical tips to the next generation of scientists.



“ Striving for work-life balance does not mean you have to compromise. You can be a great clinician and an accomplished researcher without sacrificing your home life. Be ambitious and aim to achieve both.

Collaborate – rather than compete – with your colleagues and look for inventive mutually-beneficial solutions to manage responsibilities, time, commitments and goals.

”

Mr Kourosh Saeb-Parsy

“ The reality is I love doing research just as much as I love my life outside of research – my family, friends, enjoying London and growing vegetables just outside the city. ”

Dr Cristina Lo Celso



Reflecting on their personal journey also affords researchers the opportunity to explore and share the way their passions and achievements outside of work have influenced their careers.

We believe that time outside of work has the potential to nourish creativity, build resilience, and give fresh perspectives on existing problems, precisely the skills that result in the best quality research. A life outside science is not an extra, but an integral part of who we are as scientists.

Our campaign provides a hub for biomedical and health researchers to describe their personal journeys and their attempts to blend their work and home lives. We hope this will provide a valuable resource for those currently working in the field and those considering medical science as a career.

Our #MedSciLife activities include a website, photo exhibition, social media campaign and events.

Read more on our website: www.medscilife.org

Join the conversation on Twitter [#MedSciLife](https://twitter.com/MedSciLife)



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