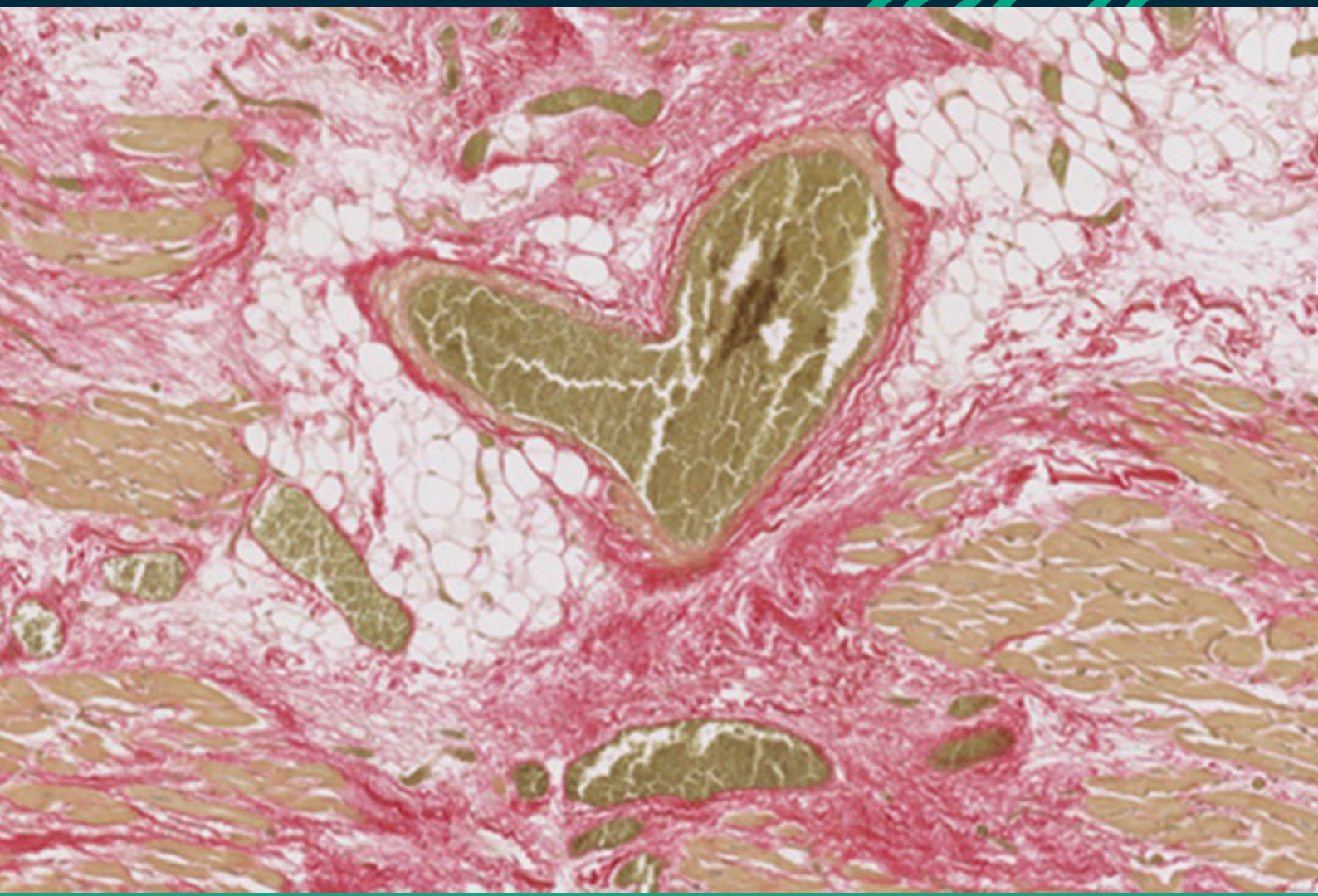
St George's
University of London

# RESEARCH DAY

## Showcasing Research Excellence at St George's

Wednesday 7 December 2022



# Welcome to St George's, University of London Research Day 2022

Welcome to the 2022 St George's Research Day, a major highlight of our University calendar. It has been a good year for research at St George's, with success in both Research Excellence Framework (REF), and Knowledge Exchange Framework (KEF). St George's was ranked joint 8th in the country for research impact out of 129 institutions, with good quality research outputs. Our QR funding has gone up by 58% as a result. We will be hearing this morning from three of the researchers who had key roles in some of the world-leading impact cases submitted to REF.

I am really looking forward to the poster session where the best of what we do will be on display. Thank you to all of you who submitted a poster. Maybe yours will be a prize winner in a category or even be the overall best poster which will be selected for the prestigious Chrissie Fenske award of £1,000.
The St George's Outstanding Research Awards continue to generate a very high level of competition and highlights the very best research taking place across the University as well as the emerging talents at the level of postdoc and lecturer, two groups that I am keen to support. The panel had a very difficult job choosing the award winners, and it will definitely be worth attending the awards ceremony followed by presentations from the winners this afternoon; might it be you in 2023?

Finally, I am delighted that the Thomas Young Lecture will be given this year by Professor Sir Mark Caulfield. This is a highlight of the day and he will be talking on "Transforming Precision Healthcare: Making personalised diagnoses and tailoring treatment."

Enjoy the day!

**Professor Jonathan Friedland**

Deputy Vice-Chancellor (Research and Enterprise)
and Professor of Infectious Diseases

# Exhibitors Research Day 2022

This event has been supported by the following exhibitors:

# St George's, University of London
# Research Day 2022
# Wednesday 7 December 2022

| | |
|---|---|
| 9:45-9:50 | ***Welcome and the REF from Jon Friedland***, The Curve Lecture Theatre |
| 9:50-10:40 | ***"Impact and Arrivals" session,*** The Curve Lecture Theatre (Hunter Wing, L0)<br>***Presentations of two of our Impact Cases from the REF and two of our New Arrivals***<br>**Jason Hinds:** 'Novel molecular serotyping technology advances worldwide pneumococcal vaccine impact and development.'<br>**Sanjay Sharma:** 'Preventing sudden death in the best by refining a cheap test!'<br>**Marta Futema:** 'Finding FH to prevent coronary heart disease'<br>**Lindsay Bearne**: 'Stepping forwards: supporting walking behaviour change in people with peripheral arterial disease'<br>**Kirsty Le Doare:** 'Driving strategies to prevent neonatal Group B streptococcal infection'. |
| 10:40-14:00 | ***Poster Presentations*****,** Boardrooms and Alastair Hunter Room (Hunter Wing, L2)<br>***Lunch***, Student Union Bar (Hunter Wing, L2) |
| 14:30-14:45 | ***Prizegiving,*** The Curve Lecture Theatre (Hunter Wing, L0) |
| 14:45-15:45 | ***St George's, Research Awards,*** The Curve Lecture Theatre (Hunter Wing, L0)<br>***Presentation by winners in each category***<br>Outstanding Research Publication (2021/22): Catrin Moore and Tom Harrison<br>Outstanding Postdoctoral Research Scientist Award: Mohammed Hudda<br>Excellence in Public/Civic Engagement in Research: Fiona Jones<br>Prize for Outstanding Research Achievement by a University Lecturer: Christopher Carroll |
| 15:45-16:00 | ***Break*** |
| 16:00-17:00 | ***The Thomas Young Lecture: Professor Sir Mark Caulfield,***<br>The Curve Lecture Theatre (Hunter Wing, L0)<br>Transforming Precision Healthcare: Making personalised diagnoses and tailoring treatment |
| 17:00-19:00 | ***Reception,*** H0.1/H0.2 (Hunter Wing, L0) |

# Thomas Young Lecture 2022

# Sir Mark Caulfield

Professor Sir Mark Caulfield is Professor of Clinical Pharmacology at Queen Mary University of London and the Vice Principal for Health for Queen Mary's Faculty of Medicine and Dentistry.

Professor Caulfield graduated in Medicine in 1984 from the London Hospital Medical College and trained in Clinical Pharmacology at St Bartholomew's Hospital where he developed a research programme in molecular genetics of hypertension and translational clinical research.

At Queen Mary University of London Professor Caulfield has made substantial contributions to the discovery of genes related to blood pressure, cardiovascular health, cancer, and rare diseases. His research has changed national and international guidance for high blood pressure. He was Director of Queen Mary's William Harvey Research Institute between 2002 and 2020 and was elected to the Academy of Medical Sciences in 2008.

He has won the Lily Prize of the British Pharmacology Society, the Bjorn Folkow Award of the European Society of Hypertension 2016, and the Franz Volhard Award of the International Society of Hypertension in 2018.

Professor Caulfield was appointed Chief Scientist for Genomics England in 2013, charged with delivery of the 100,000 Genomes Project on whole genome sequencing in rare disease, cancer, and infection.

At Genomics England, he was instrumental in delivering the 100,000 Genomes Project which has delivered life-changing results for many patients. He has also worked with NHS England to co-create the National Genomic Test Directory, which offers equitable access for 56 million people to appropriate genomic tests. Professor Caulfield was awarded a knighthood in 2019 for his leadership of the 100,000 Genomes Project.

He is a member of the Barts Health NHS trust Board and is the President Elect of the British Pharmacological Society.

# “Impact and Arrivals” session

## Dr Jason Hinds

‘Novel molecular serotyping technology advances worldwide pneumococcal vaccine impact and development.’

Dr Jason Hinds is a Reader in Translational Pathogen Genomics in the Institute for Infection and Immunity and co-founder of BUGS Bioscience, a St George’s not-for-profit spin-out company. Dr Hinds completed his PhD at the London School of Hygiene and Tropical Medicine investigating targeted gene replacement in *Mycobacterium tuberculosis*. His career at St George’s started in 1999 on a “proof-of-principle” project developing DNA microarrays for the first pathogen genomes available. This expanded into BµG@S (Bacterial Microarray Group at St George’s), a multi-collaborative resource within the Wellcome Trust’s Functional Genomics Initiative, supporting a large network of international researchers working broadly in the area of bacterial pathogenesis. Dr Hinds and team have embraced ongoing advances in genomics technology in research projects for a range of infectious diseases, particularly focused on the translational application of pathogen genomics to diagnosis, vaccine surveillance or real-time clinical investigations.

## Sanjay Sharma

‘Preventing sudden death in the best by refining a cheap test!’

Professor Sanjay Sharma O St John, BSc (Hons), MD, FRCP, FESC

Sanjay Sharma is Professor of cardiology at St George’s, University of London and St George’s NHS Foundation Trust. His interests include heart muscle disease, sudden cardiac death in the young, and sports cardiology for which he has an international reputation and over 350 publications on PubMed (h index 88). He regularly lectures at major scientific meetings and is now considered as one of the most prolific cardiologists in the world in his field of research.

Professor Sharma leads a large tertiary inherited cardiac diseases programme serving Southeast England to manage young patients with cardiomyopathy and ion channel diseases. He is the director for the largest sports cardiology unit in the UK which is responsible for athletes with potentially serious cardiac diseases from the English Football Association, rugby league, Lawn Tennis Association and the English Institute of Sport.
He is the cardiology advisor for the British rowing team, Sky cycling squad and is the chairman for the expert cardiac committee for the Football Association. He is medical director of the London marathon and has been commended for providing one of the best medical services for endurance events in the world. He was awarded membership of Venerable Order of St John for his services to St John Ambulance for supporting the medical welfare of the runners. Professor Sharma was lead cardiologist for the 2012 London Olympics and provided medical services for all endurance sports.

## Marta Futema

'Finding FH to prevent coronary heart disease'

Marta Futema is Lecturer in Cardiovascular Science at the Cardiology Research Centre at St George's, University of London. Her research overarches genetics, bioinformatics and functional genomics approaches to understand causes of inherited cardiovascular diseases. She has a strong focus on genetic aetiology of Familial Hypercholesterolaemia (FH), from rare variants to polygenic risk scores. Her work has had an impact on the UK clinical guidelines on FH, the NICE Guidelines.

Dr Futema qualified in Medical Biotechnology from University of East London, followed by PhD in Cardiovascular Genetics from UCL Genetics Institute, University College London. She held two postdoctoral positions at UCL before taking up the independent research post at St George's in 2021. She remains as an honorary Senior Research Fellow at UCL.

Marta contributes to postgraduate teaching at St George's, UCL and Queen Mary University of London, which includes supervision of PhD students.

## Lindsay Bearne

'Stepping forwards: supporting walking behaviour change in people with peripheral arterial disease'

Lindsay Bearne joined the Population Health Research Institute as Professor of Physiotherapy & Rehabilitation in August 2022. Lindsay's research focuses on the consequences and rehabilitation of people with long-term conditions and the translation of evidence into practice. Alongside her role as St George's, Lindsay is a Senior Research Fellow in knowledge mobilisation at the National Institute for Health and Care Research.

## Kirsty Le Doare

'Driving strategies to prevent neonatal Group B streptococcal infection'.

Kirsty Le Doare is a Professor of Vaccinology and Immunology at St George's, University of London seconded to MRC/UVRI@LSHTM research unit, Uganda and chief investigator for the SGUL@MUJHU maternal vaccines and seroepidemiology of Group B Streptococcus (GBS) studies. She has over 10 years of experience investigating the interactions between hosts and pathogens during the neonatal period, particularly Group B Streptococcus (GBS). Her primary interest is in understanding why some babies get very ill and die from GBS disease and how we can harness protection transferred from mother to her baby via the placenta and in breastmilk. Her groups in Uganda and the UK use a variety of approaches to study GBS and other neonatal pathogens such as E. coli and Klebsiella, ranging from clinical studies and whole genome sequencing, to in vitro and in vivo models.

# St George's Research Awards

**Outstanding Research Publication (2021-22): Catrin Moore, 'Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis'**

Dr. Moore led the Global Research on AntiMicrobial resistance (GRAM) project based in the Big Data Institute, University of Oxford. Partnered with the Institute for Health Metrics and Evaluation (IHME) and Tropical Medicine, they analysed global data to estimate the global burden of antimicrobial resistance (AMR).

Dr Moore is a member of the World Health Organization Advisory Group on Critically Important Antimicrobials (AG CIA) for Human Medicine and a mentor for Fleming Fund Fellows in Eswatini.

Now based at St George's, University of London she works closely with researchers in several LMICs on the AMR Data to Inform Country Antibiotic Guidance and Local Action (ADILA) project.

She's passionate about reducing the burden of AMR in the community through meaningful, simple, and sustainable interventions such as the use of diagnostic tools, training, and communication in the in low- and middle-income countries (LMICs).

**Tom Harrison, 'Single- Dose Liposmal Amphotericin B Treatment for Cryptococcal Meningitis'**

Tom Harrison is Professor of Infectious Diseases and Medicine, Deputy Director of the Institute for Infection and Immunity, and Lead for the Centre of Global Health. He is also Honorary Consultant at St George's University Hospitals NHS Foundation Trust.

He leads a clinical and laboratory research programme on the prevention and treatment of cryptococcal meningitis with colleagues from St George's, and in collaboration with other UK institutions, and colleagues across study sites in Sub-Saharan Africa. As a member of the InterTB consortium, he is also involved in phase II and III clinical trials aimed at simplifying and reducing the duration of treatment for pulmonary tuberculosis through the use of high dose rifamycins and leads the hospital multi-drug resistant (MDR) TB service and research programme**.**

## Outstanding Postdoctoral Research Scientist Award: Mohammed Hudda

Mohammed Hudda is a Senior Research Fellow in Applied Medical Statistics with research interests in childhood obesity, health inequalities and statistical methods for clinical risk prediction. His primary research has focused on exploring novel techniques to assess childhood adiposity, which provide improved assessment over BMI, the most widely used adiposity marker. In two recent papers published in the BMJ, Dr Hudda and colleagues describe the development and extensive external validation of an algorithm to assess childhood lean and fat mass, using only readily available information on weight, height, sex, age and ethnicity. Dr Hudda's current research seeks to investigate the long-term associations between childhood adiposity and adult chronic disease risk.

## Excellence in Public/Civic Engagement in Research: Fiona Jones

Fiona is Professor of Rehabilitation Research at St George's, University of London, and has led multiple studies to evaluate self-management approaches within healthcare teams including stroke, acute brain injury and major trauma. In 2013 Fiona set up a social enterprise, 'Bridges Self-management', which is an approach to self-management co-delivered with people living with complex long-term conditions and used by more than 800 acute and community rehabilitation teams across the UK.

Fiona has expertise in mixed methods and participatory research, co-production, and improvement/implementation science. Her focus is on co-design and working in partnership with patients, families, and clinical teams to develop and implement self-management training, interventions, and resources. She currently supervises PhD students based in the UK and Sweden.

In 2014, Fiona led an NIHR funded study to evaluate the use of Experience–Based Co-Design to explore ways to increase therapeutic activity in stroke units and is currently Co-lead for the LISTEN project (Long Covid Personalised Self-managemenT support- co-design and EvaluatioN). In 2017 Fiona was awarded an MBE for services to Stroke Rehabilitation.

## Prize for Outstanding Research Achievement by a University Lecturer: Christopher Carroll

Chris completed a PhD in Molecular Medicine at University College London followed by postdoctoral work at the FinMIT Centre of Excellence for Mitochondrial Research in Helsinki, Finland. Chris joined St George's, University of London in 2017 as a Lecturer in Human Genetics in the Molecular and Clinical Sciences Research Insititute and is investigating the genetic basis of rare neurological disorders and mechanisms of mitochondrial dysfunction in disease.

# Poster Abstracts 2022

# Session 1, 11:00–12:00

**1. Mr Alexander Alamri**

A rare case of transient mutism following bilateral anterior cingulotomy for intractable cancer pain.

*Alamri, A., Geranmayeh, F., Ishihara, B., Hart, M., Pereira, E.*

Introduction: In a subset of advanced cancer pain patients with diffuse pain syndromes, cingulotomy can be a safe and effective treatment option. Prevailing risks include memory deficits and mood disorder, however we present a rare case of transient mutism following bilateral anterior cingulotomy.

Methods: A 63 years-old female with debilitating pelvic pain due to sacral thyroid metastases underwent bilateral anterior cingulotomy. She underwent clinical neuropsychological assessment preoperatively and repeated 1- and 6-months post operatively, together with quantitative analysis of speech. Recovery from post-operative transient mutism was investigated quantitatively and qualitatively.

Results: Radiofrequency thermocoagulation with two stacked lesions was performed without surgical complications. Visual analogue scale pain measurements reduced from 8/10 pre-operatively to 0/10 post-operatively at three months with all analgesia successfully weaned. Immediately post-operatively the patient developed severe non-fluent aphasia with additional severe attentional impairments. Quantitative analysis of speech revealed a speech rate of 2.99 words/minute (single word utterances with word-level error rate of 5.89%. At 1 month post-operatively the speech was characterised by occasional single word utterances. This improved over the subsequent months. There was an improvement in the number of word errors produced over time (primarily, phonemic errors) and utterance level errors then diminished from month 2 post-operatively. At 6 months pain levels remained significantly improved but there remained a significant reduction in semantic and verbal fluency scores.

Conclusions: Bilateral anterior cingulotomy can cause severe overt speech production impairment that can recover partially within 1 month. There can be progressive improvement in speech and language metrics which reached a plateau at 5 months in this case.

**2. Miss Rossul Al-Bahadili**

Antimicrobial susceptibility and characterisation of host-pathogen interactions amongst diverse neonatal K. pneumoniae isolates

*Al-Bahadili, R., Lim, S., Le Doare, K*

Introduction K. pneumoniae is a major cause of hospital acquired infections worldwide, high rates of intestinal carriage are seen among hospitalized patients. Neonates are at risk of acquiring opportunistic pathogens early in life. Neonatal sepsis causes half a million deaths annually and K. pneumoniae accounts for 20% of those cases. With the rising threat of antimicrobial resistance, the WHO has listed K. pneumoniae as a priority pathogen to drive efforts towards understanding its pathogenicity and immunological response to its infection.

Aim To characterise the antimicrobial resistance and host-pathogen interactions of a diverse range of Kp isolates.

Methods A total of 49 isolates were obtained from infants presenting with signs and symptoms of sepsis in the United Kingdom (n=15) and Uganda (n=34). Minimum inhibitory concentrations were determined using agar

microdilution. Caco2 cells were infected with 20-25 mid-log phase bacteria per cell. Adhesion was determined after 30 minutes incubation and invasion after colistin protection assay. Bacteria were enumerated by plating out appropriate dilutions on non-selective agar. Rates were calculated as percentages of surviving bacteria (CFU/mL) based on the original inoculum. Using permeable tissue culture support, invasive isolates were investigated for their ability to translocate through differentiated intestinal epithelial cells.

Results All Ugandan isolates were resistant to gentamicin. 21 Ugandan isolates were resistant to cefotaxime. None were meropenem resistant. The adhesion rate for UK isolates was 5.2% vs 14.2% for Ugandan isolates. These rates correlated with lower invasion rates for UK isolates ranging between (0-0.21%) compared to 1.83% for Ugandan isolates. Invasive isolates penetrated through differentiated intestinal epithelial cells and did not seem to translocate paracellularly.

Conclusion Excessive antimicrobial resistance across major antibiotic classes is seen in Ugandan isolates when compared to the UK. There is also a higher ability to adhere to and invade through gastrointestinal lining, both issues increase pathogenicity of K. pneumoniae in neonates. A vaccine that targets the major virulence determinants may improve neonatal outcomes in this context.

**3. Miss Ianna Alberto**

Characterisation of ephrinB1 expression in the hindbrain of zebrafish in normal and Retinoic Acid depleted conditions.

*Alberto, I., Cavodeassi, F*

The most posterior part of the vertebrate brain derives from the hindbrain. During embryonic development, this portion of the neural tube becomes segmented in blocks of neural tissue called rhombomeres. Hindbrain segmentation is essential for the correct spatial organisation of hindbrain neuronal derivatives.

Hindbrain segmentation is controlled by the activity of several signalling pathways, which establish activity gradients along the rostro-caudal axis of the structure. The Retinoic Acid signalling pathway is at the top of the gene regulatory network that controls this process. Understanding how hindbrain segmentation is controlled by this gene regulatory network requires manipulating the activity of the genes involved in the process and the analysis of the effect of these manipulations on downstream molecular effectors of segmentation.

Ephrin receptors and their ligands comprise a large family of molecules that are expressed in dynamic and complementary patterns during embryonic development. Ephrin signalling acts downstream of the gene network controlling hindbrain segmentation, to maintain rhombomere integrity. Segmental expression in the hindbrain has been reported for some of the components of this family of proteins. Here, we examine the expression pattern of the Ephrin ligand efnB1 during zebrafish hindbrain patterning. We show that efnB1 is expressed in the zebrafish hindbrain throughout embryogenesis, but a clear segmental expression pattern is only detected transiently at early stages of hindbrain development. Manipulation of Retinoic Acid activity by treatment with a retinoic acid receptor antagonist leads to widespread overexpression of efnB1 in the hindbrain.
This suggests that efnB1, as other components of the Ephrin signalling pathway, may be under the control of the hindbrain segmentation molecular network.

**5. Mr Damion Bailey**

Professional Identity and Role Perception of Nuclear Medicine Technologists Working in a Multi-Disciplinary Workforce – An Exploratory Qualitative Study

*Damion Bailey*

Introduction- Nuclear Medicine Technologists (NMT's) produce diagnostic images using radioactive substances and are a multi-disciplinary workforce that is primarily composed of Radiographers and Clinical Technologists. Understanding a workforce can promote safer practice and facilitate professional development. This can be done by exploring professional identify (an individual's identity in relation to their professional group) and role perception (an individual's view of their role in a particular workplace or area of practice). A literature search did not identify any research that investigated the professional identity of NMT's, therefore this dissertation aims to address this gap.

Aim- To explore and gain an understanding of the professional identity and role perception of Nuclear Medicine Technologists.

Methodology and Methods- Ten NMT's were recruited from a large NHS Trust. Utilising the established methodology of Qualitative Description, data was obtained using semi-structured interviews and analysed using inductive Thematic Analysis.

Findings- Four themes were identified: "Becoming the Unexpected" which detailed various training pathways that participants undertook; "Caring with Science" which described the NMT's role and defined a professional identity of "provider of care" and "user of science and technology"; "Same View, Different Lens" which portrayed how Radiographers and Clinical Technologists practise as team of NMT's; and "Confirmation of Professional Self" which presented how individuals view their professional status.

Conclusions and Recommendations- NMT's consider their role to be highly specialised, multi-faceted and patient-centred. They base their professional status on the nature of their role and their university-level education. They work together under the umbrella title of NMT with a dual professional identity of "provider of care" and "user of science and technology". However, they may have an individual identity of Radiographer or Clinical Technologist that is determined by their training pathway. Radiographers and Clinical Technologists are regulated by statute or via a voluntary system respectively, and this difference may have an impact on future of the NMT. Therefore, further research is recommended to continue to explore the identity of NMT's, their role in healthcare, their education and training, and the need to harmonise regulatory regimes of NMT's.
Keywords: Nuclear Medicine Technologist; Clinical Technologist; Radiographer; Professional Identity; Role Perception.

**6. Miss Summayah Beg**

Prediction of Adverse Perinatal Outcomes in Dichorionic Diamniotic Twins with Fetal Growth Restriction Using Uterine Artery Doppler Assessment

*Summayah Beg, Smriti Prasad, Erkan Kalafat, Asma Khalil*

Objective: In singleton pregnancies, abnormal uterine artery Doppler is moderately predictive of adverse perinatal outcomes. The objective of this study was to investigate the predictive ability of abnormal uterine artery Doppler at the time of diagnosis for adverse perinatal outcomes in dichorionic diamniotic (DCDA) twins with fetal growth restriction(FGR).

Design: Retrospective cohort study

Methods: We included all consecutive DCDA twins with FGR classified according to Delphi consensus (cases) and DCDA twins with normal growth (controls). Early onset or late onset FGR was defined as onset of FGR before or after 32 weeks gestation respectively. Mean uterine artery Pulsatility Index were converted to percentiles and MoM values using dichorionic twin-specific reference charts. Abnormal uterine artery Doppler was defined as mean uterine artery pulsatility index > 95th percentile. The primary outcome was a composite of adverse perinatal outcomes defined as presence of any of the following – stillbirth, intrauterine death, preterm birth <34 weeks, admission in to the neonatal unit or any neonatal morbidity. Antenatal and neonatal data were extracted from electronic case records on an excel datasheet. Standard statistical methods were employed for comparison of the groups.

Results: 89 DCDA twins with FGR classified according to Delphi consensus and 643 DCDA twins with normal growth were included in the study. Mean uterine artery PI MoM was not significantly different between normally grown and growth-restricted fetuses (0.84 vs 0.87, P=0.772). Among growth-restricted fetuses, mean uterine artery PI MoM was not significantly different between those who had composite adverse outcomes compared to those who did not (0.81 vs 0.90, P=0.823). Mean uterine artery PI MoM was not a good predictor of composite adverse outcomes in growth-restricted twin pregnancies (AUC: 0.60, 95% CI: 0.51 – 0.68).

**7. Miss Summayah Beg**

Twin Pregnancies with Complications: The impact on Neurodevelopment. A Study via Registry Follow up (TWINS-RF)

*Summayah Beg, Asma Khalil, Smriti Prasad*

Objective: The prevalence of adverse neurodevelopmental outcomes and the identification of risk factors in both complicated and uncomplicated monochorionic and dichorionic twin pregnancies are yet to be established. The objective of this study was to compare the incidence of adverse neurodevelopment outcomes after one year of age in uncomplicated monochorionic and dichorionic twin pregnancies and pregnancies affected by TTTS, TAPS, sFGR, TRAP and sIUD.

Design: Prospective Case Control Study

Methods: The study population was divided into controls (uncomplicated DCDA & MCDA twin pregnancies) and cases (MCDA twin pregnancies complicated by either TTTS, sFGR, TAPS, TRAP or sIUD). Chorionicity was determined at the time of booking ultrasound and women who had pregnancies where one or both twins born alive were included. Mothers of children aged between 12 to 60 months at time of assessment were asked to complete the relevant ages and stages questionnaires (ASQ) to assess the childs neurodevelopment; a score of more than 2 SD below the mean score was considered abnormal. Maternal data and perinatal outcomes were obtained from viewpoint and the Euroking E3 system. The primary outcome measure was an abnormal ASQ-3 defined by a score 2 standard deviations lower than the mean, for a domain.

Results: 604 eligible pregnant women were invited to participate in the study, 327 ASQ-3 questionnaires were completed. 117 (35.78%) were classified as the cases whilst 210 (64.2%) remained as controls. The overall prevalence of an abnormal ASQ-3 score in children with complicated MCDA twin pregnancies (cases) was significantly higher and almost double than that in uncomplicated MCDA/DCDA twin pregnancies (14.53%;17/117 versus 7.62%;16/210, p = 0.047). Children born of complicated MCDA twin pregnancy also showed significantly higher rates of impairment of the gross motor domain compared to the control group (8.55%; 10/117 versus 2.86%; 6/210, p = 0.022). Complicated MCDA twin pregnancies which underwent prenatal intervention (fetoscopic laser, bipolar cord coagulation, intrafetal laser) had significantly higher rates of abnormal ASQ-3 score compared to those which did not have any prenatal intervention (28.07%; 16/57 versus 1.67%; 1/60, p = 0.0001).

**8. Miss Rebecca Beni**

Beyond the tip of the iceberg: A meta-analysis on the anatomy of the clitoris

*Beni, R. ,Longhurst, G.J.*

Introduction: Historically, the clitoris has been considered a shameful structure and not clinically relevant. Empirical data regarding its anatomy are lacking.

Aim(s): The aims of this study are to collate data on the anatomy of the clitoris and underline the lack of representation within the literature.

Materials and Methods: A systematic review and meta-analysis was performed on Ovid Medline and Embase. Descriptions of clitoral structures were extracted from different types of studies, in addition to 32 anatomical textbooks. A meta-analysis was performed to calculate the average and range of clitoral structures. A statistical analysis was performed to compare measurements from different study modalities.

Results: Within the textbooks, the word 'penis' was mentioned 2.6 times more than the word 'clitoris'. Discrepancies in anatomical descriptions were noted. Nine textbooks reported the distance between the external urethral meatus and the clitoris (20.00–30.00 mm) and two reported the combined length of the glans and body (30.00 mm;20.00-40.00 mm). Data were extracted from 31 studies. The average length and range of the glans (8.60 mm; 0.5-35 mm), body (28.14 mm; 13.00 mm-59.00 mm), crura (48.43 mm; 25.00 mm-90.00 mm), bulb of the vestibule (54.00 mm; 13.00 mm-70.00 mm), prepuce (23.84 mm; 5.00 mm-40.00 mm), and frenulum (9.5 mm; 5.00 mm-12.00 mm) were calculated. No statistical difference was found between the different imaging modalities.

Conclusion: The clitoris is an underrepresented structure in textbooks. The variations in clitoral measurements must be disseminated widely.

**9. Mr Rohan Bhate**

Identification of novel muscle stem cell gene/biomarker dysregulation in congenital muscular dystrophies

*Bhate,R., Quaye,L., Malik, S., Pomeranz, G., Pittman, A., Osborn,D.*

The high functional demand on skeletal muscle can lead to injuries associated with trauma or overuse. Failure to successfully restore muscle function leads to reduced fitness, health and longevity. Vertebrates have a robust mechanism to regenerate and repair damaged muscle, mediated by muscle stem cells (MuSCs). The failure to restore damaged muscle has been attributed to defects in MuSC behaviour. Indeed, MuSC dysfunction is now considered a major contributor to muscle related disorders, such as Duchenne Muscular Dystrophy (DMD). However, the genetic changes that activate MuSCs to repair damaged muscle are not well defined. To address these issues, we recently analysed publicly available zebrafish single cell RNA sequencing (scRNASeq) data, identifying genes involved in MuSC character. We identified 18 and 28 novel genes expressed specifically in quiescent and activated MuSCs, respectively, and four genes expressed in both. We hypothesize that dysregulation of some of these MuSC candidate genes underlie defects associated with DMD muscle repair. To investigate expression of our putative MuSC genes during muscle damage, we developed a novel zebrafish-CRISPR DMD model. We have screened 19 putative MuSC genes for differential expression in zebrafish DMD crispants. Six genes (myca, tuba8l3, thbs4b, vwde, entpd1, fabp3) have demonstrated reproducible upregulation in diseased muscle, compared to healthy controls. Taken together, these data are providing novel pathways to target for novel therapeutic interventions for patients sufferinf with DMD.

**10. Dr Raghav Bhatia**

Sudden cardiac death during exercise in young individuals with hypertrophic cardiomyopathy

*Bhatia RT, Westaby J, Behr E, Papadakis M, Sharma S, Finocchiaro G, Sheppard MN*

Background: Sudden cardiac death (SCD) in young individuals and athletes is caused by hereditary cardiac conditions, including cardiomyopathies such as hypertrophic cardiomyopathy (HCM). Although historically HCM has been reported as the predominant cause of SCD in young athletes, it is unclear as to what degree exercise is a trigger for possible fatal arrhythmias.

Aim: To report on the circumstances of SCD in a cohort of young individuals aged ?10 and <30 whose autopsy was consistent with HCM.

Methods: We reviewed 6860 consecutive cases of SCD referred to our specialist cardiac pathology centre between 1994 and 2020. SCD was defined as death from a cardiovascular cause within 12 hours of apparent well-being. All cases underwent detailed autopsy evaluation of the heart, including a minimum of 10 tissue blocks for histological analysis. HCM was defined by the presence of increased heart weight or increased wall thickness and significant myocyte disarray.

Results: 264 (4%) cases of SCD were due to HCM. Our cohort of young decedents comprised of 66 individuals (mean age 21±5years, males 76%). By-stander cardiopulmonary resuscitation was performed in 70% of cases and 23% of cases received automatic external defibrillation. For the majority (n=52, 79%) SCD was the first manifestation of HCM. The average heart weight was 507±152g and left ventricular (LV) fibrosis was found in 28 (42%) cases. Death was more common between 16 and 20 years of age (n=24). Death occurred during exertion in 26 (39%) individuals and at rest or during daily activities in the remaining 40 (62%). Younger individuals between 10–15 years of age died mostly during exercise (80%), in other age groups death occurred mainly at rest (33% in age group 16–20 years, 30% in age group 21–25 years, 33% in age group 26–30 years).

Conclusion: In the context of HCM, our findings suggest that individuals aged 10-15 years are the most vulnerable of exercise-related-SCD. This exemplifies the role of preventative cardiac screening in young individuals who might be harbouring quiescent cardiac conditions associated with SCD. Early diagnosis may facilitate comprehensive risk-stratification and tailored exercise prescription with the potential to prevent SCD.

**11. Dr Raghav Bhatia**

Mitral valve abnormalities in decedents of sudden cardiac death due to hypertrophic cardiomyopathy and idiopathic left ventricular hypertrophy

*Bhatia RT, Khoury S, Westaby J, Behr E, Papadakis M, Sharma S, Finocchiaro G, Sheppard MN*

Background: The sole identification of left ventricular hypertrophy (LVH) in a young individual that died suddenly may often lead to an erroneous diagnosis of hypertrophic cardiomyopathy (HCM).

Aim: To report on the prevalence and nature of mitral valve (MV) abnormalities, in a cohort of sudden cardiac death (SCD) victims with a post-mortem examination consistent with HCM and ILVH.

Methods: We reviewed 6860 consecutive cases of SCD referred to our specialist cardiac pathology centre between 1994 and 2020. SCD was defined as death from a cardiovascular cause within 12 hours of apparent well-being. HCM was defined by the presence of LVH, in the absence of abnormal loading conditions and characterised by myocyte disarray at histology. ILVH was defined as unexplained LVH (heart weight >500g in males and >400g in females) and left ventricular (LV) wall thickness >15mm, in the absence of myocardial disarray or secondary causes of LVH.

Results: 264 (4%) cases of SCD were due to HCM (mean age 41±18 years). Ante-mortem symptoms were reported in 44 (17%) cases and for the majority (n=217, 82%) HCM was established at post-mortem. Death was attributed to ILVH in 253 (3%) cases (mean age 43±16 years). MV abnormalities were found in 58 (22%) decedents with HCM and in 13 (5%) decedents with ILVH, $p<0.001$. Amongst the cases with HCM and MV abnormalities, 15 (6%) cases had multiple MV abnormalities. These included impact lesions associated with thickening of the anterior leaflet of the MV (n=39) and degenerative changes (n=34) such as bulging and ballooning; and thickening and nodularity. Among decedents with HCM and ILVH exhibiting MV abnormalities, the former was significantly younger (38±17 versus 55±15; $p=0.001$). Myocardial fibrosis was observed in 162 (61%) cases of HCM and 99 (39%) cases of ILVH, $p<0.001$.

Conclusion: MV abnormalities are four-fold more common in individuals with HCM than those with ILVH and may be considered as additional macroscopic features to differentiate between these two entities.

**12. Dr Raghav Bhatia**

Prevalence and diagnostic significance of de-novo 12-lead ECG patterns following COVID-19 infection in elite soccer players

*Bhatia RT, Malhotra A, MacLachlan H, Gati S, Marwaha S, Chatrath N, Fyyaz S, Aleixo H, Al-Turaihi S, Basu J, Babu B, Cooper R, Dhutia H, Daems J, Ferrari F, Hattum J, Kasiakogias A, Kenny A,, Khoury S, Miles C, Oxborough D, Quazi K, Rakhit D, Sharma A, Va*

Background: The identification of athletes with cardiac inflammation following COVID-19 can prevent exercise fatalities. The efficacy of pre- and post-COVID-19 infection 12-lead electrocardiograms (ECGs) for identifying athletes with myopericarditis has never been reported.

Aim: To assess the prevalence and significance of de-novo ECG patterns following COVID-19 infection.

Methods: In this multicentre study, between March 2020–May 2022, we evaluated consecutive athletes with COVID-19 infection. ECGs were reported in accordance with the International recommendations for ECG interpretation in athletes. Given that some repolarisation changes overlap between myopericarditis and athlete's heart, we considered the following ECG patterns as abnormal if they were not detected on the pre-COVID-19 infection ECG: PR-segment depression, new J-point and ST segment elevation (?0.2mV in the precordial leads and ?0.1mV in the limb leads), low QRS voltages, complete right bundle branch block, QRS fragmentation, new ST-segment depression, new T-wave inversion, biphasic T-waves and a reduction in the T-wave amplitude by 50% or T-wave flattening. Athletes exhibiting de-novo ECG changes underwent cardiovascular magnetic resonance (CMR) scans. One club mandated CMR scans for all players (n=30) following COVID-19 infection, despite the absence of cardiac symptoms or de-novo ECG changes.

Results: 511 soccer players (median age 21-years, IQR:18-26-years) were included. 17 (3%) athletes demonstrated de-novo ECG changes, which included, reduction in T-wave amplitude in the inferior and lateral leads (n=5), inferior leads (n=4) and lateral leads (n=4); inferior T-wave inversion (n=7), and ST-segment depression (n=2). 15 (88%) athletes with de-novo ECG changes revealed evidence of inflammatory cardiac sequalae. Athletes who underwent a mandatory CMR had normal findings. Athletes revealing de-novo ECG changes, had a higher prevalence of cardiac symptoms (71% v 12%; $p<0.0001$) and longer median symptom duration (5-days, IQR:3-10) compared with athletes without de-novo ECG changes (2-days, IQR:1-3; $p<0.001$). Among athletes without cardiac symptoms, the additional yield of de-novo ECG changes to detect cardiac inflammation was 17%.

Conclusions: 3% of athletes demonstrated de-novo ECG changes post COVID-19 infection, of which 88% were diagnosed with cardiac inflammation. Most affected athletes exhibited cardiac symptoms; however de-novo ECG changes contributed to a diagnosis of cardiac inflammation in 17% of athletes without cardiac symptoms.

**13. Dr Kathryn Biddle**

Gender differences in neuropathic pain in subjects with rheumatoid arthritis and osteoarthritis

*Kathryn Biddle, Franklyn Howe, Nidhi Sofat*

Background: Evidence suggests that women experience increased pain sensitivity and neuropathic pain compared to men across a range of rheumatological conditions. The aim of this study was to characterise gender differences in pain in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) and to investigate the predictors of neuropathic pain in this cohort.

Methods: Secondary analyses were performed using data from two observational studies (Early Biomarkers for ARthritic PAIN to Guide Improved Treatments for Arthritis (ARPAIN) Study (NCT03533569) and understanding pain perception in osteoarthritis: a mechanistic study in people with knee osteoarthritis (PAPO) (IRAS ID:99426)).

Three patient groups were included in the analysis: 122 from PAPO and 68 from ARPAIN with knee osteoarthritis (OA); 19 with rheumatoid arthritis (RA) from ARPAIN. Patient measures comprised: Gender, Age, BMI, knee pain, stiffness and function measured using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and neuropathic pain measured using the painDETECT questionnaire. Mann-Witney (M-W) and Kruskal-Wallis (K-W) tests, and a General Linear Model (GLM) analysis, was used for group comparison and assessment of Gender on WOMAC and painDETECT scores.

Findings: Women comprised 71% of the patients. K-W indicated significant group differences in age ($p=0.01$) and WOMAC_P ($p=0.029$) between ARPAIN and PAPO OA patients. M-W indicated no significant differences between OA and RA groups, but significantly higher painDETECT ($p<0.001$) WOMAC_stiffness ($p=0.005$) and function ($p=0.022$) in women than men. A GLM with main effects of Gender, BMI, Age and Group indicated significant effects of: painDETECT with Gender ($p<0.001$) and BMI ($p=0.043$); WOMAC_pain with BMI ($p<0.001$); WOMAC_stiffness with Gender ($p=0.003$) and BMI ($p=0.001$); WOMAC_function with Gender ($p=0.032$), BMI ($p<0.001$) and Group ($p=0.02$). Linear modelling indicated painDETECT was strongly correlated to WOMAC_pain ($p<0.001$) with only Gender significant ($p<0.001$) with women scoring on average 3 points higher on painDETECT for the same WOMAC pain score as men.

Interpretation: Our findings suggest that women with RA and knee OA have increased neuropathic pain in comparison to men. In our cohort, neuropathic pain increases with WOMAC scores for pain, stiffness and function, however women show significantly greater painDETECT scores for any given WOMAC score. This suggests that women are at increased risk for the development of neuropathic pain. Future studies are needed to establish the distinct features of pain sensitivity in RA and OA across genders.

**14. Miss Rachel Bowsher**

Characterising air-liquid interface cultures and assessing their suitability as a 3D model of the human airways

*Rachel Bowsher, Emma-Jane Goode, Tim Marczylo, Matthew Wright, Karen Gooch, Alexis Bailey and Emma Marczylo.*

Background: We wished to examine whether environmental exposures can increase the susceptibility of the human airways to SARS-CoV-2 infection in healthy individuals. Therefore, we want to establish a model that closely mimics the human airways. Air-liquid interface(ALI) cultures are commonly used for 3D modelling of the human airways and direct exposure to airborne toxicants. Compared to primary cells, commercially available immortalized normal cell lines are cheaper, readily available and easier to maintain. Therefore, we explored the suitability of the Human Bronchial Epithelial Cell – 3KT(HBEC-3KT) line at ALI as a 3D model of the human airways.

Methods: HBEC-3KT cells were seeded at various densities and kept at ALI for up to 28 days with weekly images and trans-epithelial electrical resistance(TEER) measurements taken. Cells were harvested every seven days. RT-qPCR was performed to assess the expression of mRNA markers for ciliation, basal cells, tight junctions and mucus production.

Results: Basal cells differentiated. Mucus production was observed from day 16 but no cilia were seen. Goblet cell and ciliated cell markers were significantly upregulated whereas tight junction markers remained similar throughout the 28 days. Genes of interest were significantly increased around days 7 to 14 at ALI, compared to day 0.

Conclusions: Although differentiating, the lack of tight junctions and cilia may impact any infection rate/risk conclusions obtained when using the model. Despite this, the observed increases in genes of interest expression within 7 days suggests that the model may be more suitable than submerged culture. Hence, may be a useful tool for studying the initial changes induced by exposures as a screening mechanism for genes of interest.

**15. Miss Rachel Bowsher**

What is the association between smoking and COVID-19 susceptibility or severity?

*Rachel Bowsher, Alexis Bailey, Tim Marczylo, Matthew Wright, Karen Gooch and Emma Marczylo*

INTRO: Since COVID-19 continues to circulate, identifying those most at risk of infection/ severe disease is essential to tailor advice and treatments best suited for specific populations. Currently, any association between smokers and COVID-19 severity or susceptibility is conflicted. Hence, this systematic literature review aims to identify the overlapping signalling pathways and subsequent genes of interest that are up- or down-regulated by both respiratory viruses and smoking, vaping or nicotine.

METHOD: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, OVID and Web of Science databases were searched (1946 to Nov 2021), using two individual searches:

1) smoking (cigarette, vaping or nicotine), pathways of interest and the respiratory tract

2) respiratory viruses alongside the smoking exposure and pathways of interest

Abstracts and subsequent full texts were screened for eligibility against exclusion criteria with any discrepancies discussed and agreed. Data detailing the exposure, pathway or gene of interest, sample type and overall findings, was extracted from papers selected for inclusion. Pathway analysis was undertaken to identify those in common.

RESULTS: We identified genes and signalling pathways of interest within the respiratory tract involved in both the initial viral response and those affected by smoking, vaping or nicotine exposure. To better understand the direct effects of smoking and vaping on the susceptibility of an individual to COVID-19 and/or the severity of their symptoms experienced, further research will be undertaken. Genes and pathways identified in this systematic review will be analysed pre- and post-exposure to smoking, vaping and nicotine in vitro using an air-liquid interface model.

CONCLUSION: This systematic review and further research will identify any altered susceptibility and the risk of severe COVID-19 posed to smokers and vapers, informing Public Health Policies, highlighting vulnerable groups and providing guidance of relevance to both COVID-19 and other respiratory viruses.

FUNDING: This is funded by the UKHSA PhD Studentship Fund.

**16. Ms Megan Brown**

Development of a Prototype Device for Cervical Cancer Screening

*Brown, M.*

Cervical cancer is one of the top four most common cancers in women, predominantly caused by a persistent infection with high-risk oncogenic Human Papilloma Virus (HPV). Cervical cancer is a preventable and curable disease if detected early through regular screening. HPV DNA testing has been shown to be superior to the traditional cytology-based cervical cancer screening techniques for detecting CIN2-3 cancerous lesions. HPV based screening is a more accessible and scalable screening technique as it allows for women to self-collect their own samples, however, current HPV DNA testing requires infrastructure that is not always available is resource scarce settings. Self-sampling may be an effective method to increase engagement with HPV screening and alleviate some of the barriers to testing.

Majority of the preventable cervical cancer related deaths occur in low and middle-income countries as a result of reduced screening capacity. There is therefore a need for the development of a single use, accessible and easy to use point of care HPV DNA screening assay. QuantuMDx and St George's University of London, are developing a new point-of-care HPV DNA test using these criteria.

This non-interventional study will take place in two phases. The first is to fine-tune the algorithm of the device and assay while the second phase is an initial evaluation of the prototype device to determine the functional data and ease of use. Various clinical samples (endocervical, lower vaginal, self-collected lower vaginal and optional urine sample) will be collected from eligible patients attending the St Georges University Hospital Colposcopy clinic to enable the development and evaluation of a prototype assay and determine the positive percent agreement and negative percent agreement of the assay. Allowing for the evaluation of the instrument function and assay usability.

**17. Miss Ana Brumwell**

The role of exercise in remodelling the gut microbiome to reduce seizure frequency in epileptic patients.

*Ana Brumwell*

Epilepsy is one of the leading neurological disorders worldwide associated with devastating health consequences and yet, 1 in 3 people with epilepsy cannot gain seizure control from current treatments. Moreover, existing therapy is largely inaccessible and unaffordable in developing countries and simply littered with adverse effects which patients must tolerate, thus, further investigation into alternative treatments for epilepsy is timely.

Dysbiosis in the gut is associated with epilepsy; ketosis has proven anticonvulsant effects; and whilst the beneficial role of exercise in epilepsy was once disregarded, emerging evidence is hinting at anti-seizure effects. Thus, this literature review proposes a suggested research approach comprising of a longitudinal study following 80 epileptic patients over 40 weeks. It sets out to determine the effect of exercise intensity in modulating the gut microbiome and/or amplifying endogenous ketone concentrations, to reduce seizure frequency in epileptic patients.

16s rRNA sequencing would be used to characterise gut microbial composition, whilst faecal microbiota transplantation from high intensity exercising patients into non-exercising recipients, will establish whether a modified gut microbiome from exercise has a direct effect in reducing seizures. Alongside this, seizure frequency and ketone concentrations will be self-recorded throughout.

The findings in this study will not only help fill the gap in knowledge surrounding anticonvulsant effects of high intensity exercise but reduce the burden of anti-epileptic drugs and pave the way for an alternative treatment which is efficacious, free from limitations and accessible worldwide.

**18. Ms Aurora Campagna**

Generating novel 3D cell models for prognostics, diagnostics, and immunotherapy of prostate cancer.

*A. Campagna1,2, G. Perry3, M. Bodman-Smith2, F. Valderrama1,3,4, C. Cieza-Borrella1,4*

*1. The Prostate Cancer Biology Research Team, Centre for Biomedical Education (IMBE), St. George's, University of London*

*2. The Institute for Cancer Vaccines and Immunotherapy*

Prostate Cancer (PrCa) represents the second most common malignancy in men worldwide, accounting for more than 375,000 deaths each year. Establishment and progression of the disease are still poorly understood, and this is partly due to the lack of accurate cellular models representing the disease to develop more conclusive prognostic and diagnostic models as well as effective therapeutic strategies.

Three-dimensional (3D) culture methods, such as spheroids and organoids, allow cells to organise into structures that resemble the in vivo architecture and permit the incorporation of other cell populations such as endothelial and immune cells.

The use of gamma-delta (γδ) T lymphocytes has been proposed as an attractive immunotherapeutic approach due to their ability to direct kill tumour cells in an MHC-unrestricted manner. However, models that can faithfully recapitulate the interaction between PrCa solid tumours and γδ T cells are currently lacking.

Our group has developed organoids and spheroids which display the characteristic acinar architecture of the prostatic epithelium and recapitulate the main histological features of the prostate glands by organising in a double layer of basal and luminal cells. We are now using this model to study the infiltration of γδ T cells into spheroids resembling different PrCa stages. Our preliminary results show that, co-culture, γδ T cells can migrate against gravity towards the cancerous spheroids and infiltrate the tumour mass. This γδ T cell infiltration is significantly higher into the spheroids resembling the in-situ adenocarcinoma stage of PrCa than into the benign and metastatic ones. At the present, we are investigating in more depth this PrCa- γδ T cells interaction through the analysis of chemoattractant profiles, cell viability, cell migration and infiltration patterns and potential cytotoxicity.

Altogether will allow us to assess the potential therapeutic value of γδ T cells in PrCa.

**19. Dr Veronica Carroll**

DEPTOR downregulation by HIF/DEC1 axis leads to mTOR activation in pulmonary vasculature

*Devkumar S, Rodríguez E, Barnes P, Carroll V*

Tissue hypoxia commonly occurs in lung diseases such as chronic obstructive pulmonary disease (COPD) which can cause structural and phenotypic changes to cells of the pulmonary vasculature leading to remodelling of vessels. Vascular remodelling can ultimately result in pulmonary hypertension (PH) and right ventricular heart failure. The phenotypic changes that occur in chronic hypoxia are orchestrated by the transcription factors, hypoxia-inducible factors, HIF-1 and HIF-2. HIFs regulate genes involved in increased cell proliferation, migration, inflammation and metabolism, but the complexity of altered gene expression that leads to vascular remodelling in PH is still poorly understood.

In this study, we investigated HIF-mediated mechanisms of vascular remodelling in the pulmonary vasculature of PH patients. We found that the HIF-regulated gene, DEPTOR, which is a cell growth inhibitor, was down-regulated in patients with COPD and PH as compared to control lung. Inhibition of DEPTOR correlated with increased mechanistic target of rapamycin (mTOR) signalling in PH patients and in experiments with isolated human pulmonary artery vascular smooth muscle cells (PAVSMC). In addition, a concomitant increase in expression of inflammatory mediators was observed. Further studies revealed that the HIF-mediated suppression of DEPTOR possibly occurs through the transcriptional repressor, DEC1 (BHLHe40).

mTOR is a key mediator of vascular remodelling in PH. Our data show that hypoxia/HIFs can promote mTOR signalling in the pulmonary vasculature likely contributing to inflammation and vascular remodelling. This work furthers our understanding of the pathology of PH, which may help to uncover new therapeutic targets for this fatal disease.

**20. Prof Tom Carter**

Altered storage and function of Von Willebrand factor in human cardiac microvascular endothelial cells from recipient transplant hearts

*Athinoula Meli, Ann McCormack, Ianina Conte, James Streetley, Marlene L. Rose, Matthew J. Hannah, Justin Molloy, Peter Rosenthal and Tom Carter*

Assembly of Von Willebrand factor (VWF) into ordered helical tubules within endothelial Weibel-Palade bodies (WPBs) is required for efficient deployment of the protein at sites of vascular injury. VWF trafficking and storage is sensitive to cellular and environmental stresses that are associated with heart disease and heart

failure. Altered storage of VWF manifests as a change in WPB morphology from a rod-shape to rounded shape, and is associated with an impaired capacity to deploy VWF during secretion. In this study we examined the morphology, ultrastructure, molecular composition and kinetics of exocytosis of WPBs in cardiac microvascular endothelial cells isolated from healthy donors (controls; HCMECc) or from recipient ventricles of explanted hearts of patients with a common form of heart failure, dilated cardiomyopathy (DCM; HCMECd).
By fluorescence microscopy WPBs in HCMECc (n=3 donors) showed the typical rod-shaped morphology containing VWF, P-selectin and tPA. In contrast WPBs in primary cultures of HCMECd (n=6 donors) were predominantly rounded in shape, and lacked t-PA. Ultrastructural analysis revealed a disordered arrangement of VWF tubules in nascent WPBs emerging from the trans-Golgi network. HCMECD WPBs still recruited Rab27A, Rab3B, MyRIP and Slp4-a and underwent regulated exocytosis with kinetics similar to that seen in HCMECc. However, secreted extracellular VWF strings from HCMECD were significantly shorter than for endothelial cells with rod-shaped WPBs, although VWF platelet binding was similar. Our observations suggest that VWF trafficking, storage and haemostatic potential is perturbed in HCMEC from DCM hearts.

**21. Dr David Clark**

SARS-CoV-2 Vaccine Immunogenicity in Patients with Gastrointestinal Cancer Receiving Systemic Anti-Cancer Therapy

*David K. Lau, Maria Aresu, Timothy Planche, Amina Tran, Retchel Lazaro-Alcausi, Julie Duncan, Shannon Kidd, Susan Cromarty, Ruwaida Begum, Isma Rana, Su Li, Ali Abdulnabi Mohamed, Irene Monahan, David J. Clark, Nicholas Eckersley, Henry M. Staines, Elisab*

Background: COVID-19 is a respiratory viral disease caused by SARS-CoV-2. Understanding how antibody responses evolve over time is vital in development of new therapeutics, diagnostics and vaccines. The purpose of this study was to measure the neutralising capacity of serum from patients with gastrointestinal (GI) cancer who were receiving chemotherapy. The immunogenicity of SARS-CoV-2 vaccines in this group is unknown.

Methods: Three assays were used to measure antibody responses: an anti- SARS-CoV-2-spike assay, an anti-SARS-CoV-2-nucleoprotein assay and a pseudovirus (PsV) neutralisation assay (PsV with SARS-CoV-2 spike). Serum samples were collected at baseline, d28, d56 and d84 from 152 patients; 99 participants (65% of cohort) were vaccinated at least once prior to the study (46% received BNT162b2, 51% received ChAdOx1 and 3% undetermined). 51 participants had not received a vaccine prior to the study.

Results: Vaccine induced antibody responses increased over time in this cohort although plateaued at d40-59 for a single dose. The second vaccination resulted in high values (>75%) for both anti-S and PsV neutralization. It was observed that the pVNT80 titres waned over time following the second dose. Of the patients who were not vaccinated prior to the study, 5 (9.8%) were NP positive indicating a wild-type infection.

Conclusions: We demonstrated that patients in this cohort were able to develop effective humoral immune responses to SARS-CoV-2 vaccines. These were maintained in patients who had received 1 dose of vaccine prior to systemic cancer therapy initiation. Following a second dose of vaccine, anti-S antibody and neutralization rates were boosted and high. While neutralization titres wane post secondary vaccination in this cohort this follows that observed in healthy populations (significant reductions after 6 months).

This study should provide reassurance to patients with cancer and for informing clinicians determining cancer therapies. Notably, the duration of antibody responses is likely to be limited and booster doses are recommended.

**22. Mr Alastair Clements**

Mathematical modelling for MRSA control: can we harness phage and antibiotics to halt resistance spread?

*Clements, A; Leclerc, Q; Wildfire, J; Lindsay J; Knight, G.*

Antimicrobial Resistance (AMR) is a major problem responsible for millions of deaths annually worldwide. Infections caused by Methicillin-resistant Staphylococcus aureus (MRSA) have been estimated to kill more humans than any other drug-pathogen combination. Resistance to all antibiotic classes has been observed across MRSA populations, although no strains found are fully resistant yet. In response, public health interventions, such as antibiotic-phage therapies, are being considered to tackle infections. These treatments employ antibiotics alongside viruses called phage, which replicate by infecting and destroying bacteria, however, more research is needed to determine how therapies can be delivered effectively.

Furthermore, phage can unintentionally drive the transfer of AMR genes through a process called generalised transduction. This phenomenon is likely the leading mechanism of resistance spread in MRSA, but little research has quantified its impact. The dynamics of bacteria, phage, and antibiotics are thus complex, requiring cross-disciplinary solutions to untangle their contributing factors. Doing so is important, both for clinically relevant outputs and understanding their interactions in other environments.

This project aims to better understand the impacts of antibiotic selection, phage predation, generalised transduction, and bacterial competition on AMR dynamics in MRSA. A multidisciplinary framework will be used, integrating microbiological data from co-cultures of bacteria, antibiotics, and phage, with mathematical equations describing their interactions. Thereafter, numerical simulations of their dynamics for different scenarios can be obtained by varying initial concentrations and rates of different processes. Further experiments will be used to validate the model, before analysing it to uncover key biological relationships and potential strategies for minimising AMR spread.

The results obtained from this in vitro setting will help to inform investigations for more complex environments, in vivo systems, and for other drug-pathogen combinations. Improved understanding of AMR dynamics and evolution will ultimately improve interventions to reduce AMR and save lives.

**23. Mr Zack Croxford**

Engineering Cancer Immune Checkpoint Inhibitors for Improved Expression and Performance

*Zack Croxford*

Immune Checkpoint Inhibitors (ICIs) have revolutionized the way we treat and research cancer, achieving notable clinical success in the treatment of a variety of cancers. However, current ICIs come with a set of limitations and drawbacks. Response rates are limited and unpredictable side effects as well as acquired resistance are common . Additionally, ICIs are notoriously expensive and as a result are currently inaccessible to patients in Low and Middle Income Countries (LMIC). Here, we detail efforts to design and express a novel bispecific ICI, targeting two Immune checkpoints with a single antibody. Combination ICI treatment has been shown to synergistically increase response rates and theoretically reduce the risk of resistance. This approach is coupled with the use of Nicotiana benthamiana as an alternative production platform to mammalian cell expression systems. This method would in theory provide a cheaper alternative to current ICIs and allow patients LMICs more access to them.

Work so far has shown that bispecific ICIs can be expressed in N. benthamiana, however, more work needs to be done to analyse assembly before further characterization can be conducted.

**24. Ms Ramla Cusman**

Investigating the significance of glycolysis for fibroblast MMP-dependant tissue remodelling during Mycobacterium tuberculosis infection

*Ramla Cusman, Julia Kutschenreuter, Madeleine E. Rossanese, Deborah L. W. Chong, Jon S. Friedland*

An estimated third of the world's population is infected with Mycobacterium tuberculosis (Mtb), with a significant number of people going on to develop active tuberculosis (TB) every year. Following TB treatment, patients have an increased chance of mortality, due to the extensive lung damage that occurs during active infection, driven by numerous cells including fibroblasts, which secrete matrix metalloproteinases (MMPs) that degrade extracellular matrix (ECM). In recent years, immunometabolism has become a major field, demonstrating a link between the metabolic state of various immune cells and their functions in immunity. However, the metabolic state of fibroblasts in infection is poorly characterised.

An in vitro assay was optimised in which primary human lung fibroblasts (PHLF) were stimulated with conditioned media from Mtb-infected monocytes (CoMTb). MMP-1 and MMP-3 secretion were measured by ELISA using PHLF culture supernatants. Initial glycolysis pathway inhibition experiments using 2DG (Hexokinase inhibitor) were conducted in vitro on PHLF. Subsequently, MMP-1 secretion and gene expression were measured by ELISA and RT-PCR respectively.

MMP-1 and MMP-3 secretion from PHLF was significantly increased in response to CoMTb. Blocking glycolysis with 2DG, resulted in a reduction in MMP-1 secretion from PHLF, which was observed from as early as 24 hours. Similarly, CoMTb-induced mmp-1 gene expression was abrogated with 2DG pre-treatment.

CoMTb stimulation induces significant MMP-1/-3 secretion from fibroblasts, suggesting that cellular networks are key in driving tissue remodelling during TB infection. Furthermore, glycolysis is necessary to meet the metabolic requirements of fibroblasts following CoMTb stimulation to induce MMP-1 secretion and gene expression.

**25. Miss Anahita Dadali**

Undiagnosed breech in pregnancy: an audit from 2016 - 2021

*Dadali, A.*

Aim: This study was designed to determine whether introducing a routine third trimester scan during pregnancy can reduce the incidence of undiagnosed breech presentation in labour and its complications.

Methods: We carried out this audit of all women who delivered between 04/04/2016 and 30/09/2021 at St George's University Hospital NHS foundation trust. For the purpose of this study, retrospective data were extracted from viewpoint and E3 electronic database into excel spreadsheets. At St George's Hospital, a policy of routine third trimester scan for all pregnant women has been implemented since January 2020. Following a diagnosis of breech presentation on the scan, women are counselled about their options including ECV, planned elective caesarean section or planned vaginal delivery. If women were to decline ECV or if it were to be unsuccessful, the option of elective caesarean delivery at/from 39 weeks' gestation would have been offered.Exclusion criteria included women with multiple pregnancies, preterm deliveries (<37 weeks), congenital abnormality and those undergoing planned caesarean section for breech presentation.

Conclusion: Our audit showed that routine third trimester scan was effective in reducing the incidence of undiagnosed breech presentation in labour (RR 0.29, 95% CI 0.2 – 0.38). There was no statistically significant difference in NICU admissions following birth among the two groups (RR 0.84, 95% CI 0.55-1.28). Lastly, our results showed that patients who received routine third trimester scan were 77% less likely to have APGAR score <7 at 5 minutes (RR 0.23, 95% CI 0.14-0.38). Whilst introducing third trimester scan reduces the incidence of undiagnosed breech presentations during birth as well as improving APGAR score at 5 minutes, our study did not show statistically significant difference in NICU admissions.

**26. Miss Anahita Dadali**

Impact of Point of Care Ultrasound and routine third trimester ultrasound on undiagnosed breech presentation and perinatal outcomes

*Knights, S. Prasad, S. Kalafat, E. Dadali, A (presenter). Sizer, P. Harlow, F. Khalil, A*

Objective: To compare the impact of routine third trimester ultrasound or Point of Care Ultrasound (POCUS) with standard antenatal care, on the incidence of overall and undiagnosed breech presentation at term, and on the related adverse perinatal outcomes.

Methods: We included data from St George's (SGH) and Norfolk and Norwich University Hospitals (NNUH). Pregnancies were grouped according to whether they received routine third-trimester scan (SGH) or POCUS (NNUH). Women with multiple pregnancy, preterm birth <37 weeks, congenital abnormality and those undergoing planned caesarean section for breech presentation were excluded. The primary outcome was undiagnosed breech presentation in labour. Secondary outcomes included mode of birth and neonatal adverse outcomes. We employed a Bayesian approach using informative priors from a previous similar study; updating their estimates (prior) with our own data (likelihood). The association of undiagnosed breech presentation at birth with adverse perinatal outcomes was analyzed with Bayesian log-binomial regression models.

Results: Before and after the implementation of routine third-trimester scan or POCUS, there were 16,777 and 7,351 births in SGH and 5,119 and 4,575 in NNUH, respectively. The rate of breech presentation in labour was consistent across all groups (3-4%). In the SGH cohort, the rate of undiagnosed breech was 14.2% before and 2.8% after the implementation of universal screening ($p<0.001$). Similarly, in the NNUH cohort, the rate of undiagnosed breech was 16.2% before and 3.5% after the implementation of universal POCUS screening ($p<0.001$). Using Bayesian regression analysis with informative priors showed that the rate of undiagnosed breech was 71% lower after the implementation of universal ultrasound (RR: 0.29, 95% CI: 0.20–0.38) Among the pregnancies with breech presentation, there was also a very high probability (>99.9%) of reduced rate of low Apgar score (<7) at 5 minutes by 67% (RR: 0.23, 95% CI: 0.14–0.38).

Conclusion: Routine third trimester scan or POCUS reduce the rate of undiagnosed breech in labour, with an improvement in neonatal outcomes.

**27. Mr Jonathan De Oliveira**

A survey to assess the attitudes of St George's University of London (SGUL) MBBS students towards learning about research and developing their skills during their studies.

*De Oliveira, J., Rafi, I., Chaudhry, U., Crego, R.*

The questionnaire will assess the extent to which students felt research was valuable to their learning, barriers/facilitators towards their involvement, students' views on the current level of SGUL support received, and develop the concept of academic stretch. The survey has ethical approval and is primarily being disseminated via email, WhatsApp, in-person, in lectures and small- group teaching sessions. The survey is currently open, and we have received 83 responses from students in all years of study, with the highest number of responses from students in Final Year. Currently, results indicate a strong belief among students in the importance and value of involvement in research, and a keenness to participate should opportunities arise. Students noted a number of barriers to research participation, including time available outside the core curriculum; current level of support offered, and opportunities available, from SGUL. Students tended to disagree that the SGUL MBBS course encourages students to get involved in research, that it equips students with the required skills, and that SGUL provides accessible routes to gain experience in research. Students indicated a strong preference for receiving specific support from SGUL to gain experience doing research, and were particularly supportive of the idea of SGUL providing an updated process for highlighting available projects which are looking for medical students to support research, ?outside the core curriculum. The results from this survey will inform the basis and feasibility of a new student-researcher matching service, hosted by

the St George's University Hospitals NHS Trust Translational and Clinical Research Institute (TACRI), and contribute to academic stretch.

**28. Dr Joseph Delo**

The TIGIT immune checkpoint axis mediates T cell suppression in patients with decompensated cirrhosis

*Delo, J., Forton, D., Triantafyllou, E., Singanayagam, S.*

Background: Deaths from liver cirrhosis is now the most common cause of premature death in people aged 35-49 years. The majority of deaths are associated with bacterial infections as patients with decompensated cirrhosis are both highly susceptible to developing infections and have a poor prognosis from them. While the many defects in the innate immune system are well characterised in decompensated cirrhosis, the extent and cause of any impairment in the adaptive immune system is less well understood. Immune checkpoints constitute a complex array of receptors and ligands expressed on the surface of immune cells and are known to be key regulators of T cell function. The TIGIT immune checkpoint axis has been shown to mediate T cell dysfunction in the context of severe sepsis, cancer and chronic viral infections. We hypothesised that it mediates T cell dysfunction in decompensated cirrhosis.

Methods: Patients with decompensated cirrhosis presenting to St George's Hospital were recruited. Blood samples were collected for isolation of PBMCs (n=22), and ascitic mononuclear cells were obtained by centrifugation of ascitic fluid (n=12). Cell surface expression of the immune checkpoints in the TIGIT axis were assessed by flow cytometry: CD96 and TIGIT (inhibitory), and CD226 (stimulatory) on T cells, and the ligands CD155 and CD112 on monocytes.

T cell function was assessed by expression of exhaustion markers after 48 hours of culture with anti-CD3 stimulation, with and without anti-TIGIT blockade.

Results: Peripheral CD4 and CD8 T cells from patients with decompensated cirrhosis expressed more TIGIT and CD96 compared to healthy controls, without any change in the expression of CD226. Expression of CD155 on peripheral monocytes did not change.

Ascitic CD4 and CD8 T cells expressed yet more TIGIT and CD96 when compared to their paired peripheral T cells.

CD8 T cells from patients with decompensated cirrhosis displayed a more exhausted phenotype than healthy controls, which could be partially reversed with TIGIT blockade.

Conclusion: TIGIT axis expression on peripheral CD8 T cells from patients with decompensated cirrhosis is of a more immunosuppressive phenotype and blocking TIGIT partially rescues them from exhaustion. The TIGIT axis could therefore represent a potential immunotherapeutic target to reconstitute ant-bacterial immunity in these patients.

**29. Mr Alex Denley**

Co-occurrence of Adenomyosis and Uterine Leiomyomas in women with confirmed Endometriosis

*Denley, AJC*

Background: Endometriosis (EM), Adenomyosis (AM) and Uterine Leiomyomas (UL) are three increasingly common gynaecological disorders, share similar symptoms and pathophysiology. Previous studies have separately explored the co-existence of EM with AM and UL. However, no available literature has investigated the prevalence of both AM and UL in women with confirmed EM.

Methods: Retrospective review of patients undergoing gynaecological laparoscopy selected from a St George's Hospital theatre list. Patient hospital records and surgical notes were individually studied to retrieve patient demographics, determine EM status and assess if AM and/or UL were also present. Descriptive and statistical analysis was performed.

Results: Of 66 patients with laparoscopically confirmed EM: 22 (33.3%) had EMO, 42 (63.6%) had EA, 14 (21.2%) had EL, and 12 (18.2%) had EAL. 2/3 of women with EM also had AM, which is six times greater than the national prevalence (11.0%) within women undergoing hysterectomy. It is also significantly higher than previous estimates of prevalence (21.8%) in a similar cohort. 1/5 of women with EM also had UL, which is four times greater than the national prevalence (4.5%). This is comparable to previous reports of the prevalence (25.8%) in a similar cohort. 1/5 of women with EM had AM and UL, a notable finding of this clinical audit. There are no studies in which to compare the prevalence of the three conditions co-existing.

Conclusion: 66% of women with laparoscopically confirmed EM had co-occurrent AM and/or UL, suggesting a correlation between conditions exists. Clinical suspicion of co-occurrence should be maintained pre- and peri-operatively.

**30. Dr Angela Donin**

A cross-sectional survey of circulating vitamin D concentrations in a multi-ethnic population of 9-10-year olds; can they explain ethnic difference in early type 2 diabetes precursors?

*Donin, A.S., Nightingale, C.M., Sattar, N., Fraser, W., Owen, C.G., Cook, D.G., Whincup, P.W.*

Background: In the UK, low circulating vitamin D (25[OH]D) concentrations occur particularly in people of ethnic minority origin and are associated with higher risks of type 2 diabetes, cardiovascular disease and all-cause mortality, although causality remains uncertain. However, little is known about the associations between circulating 25(OH)D concentrations, type 2 diabetes and cardiovascular risk precursors in children, particularly in ethnic minority populations.

Aim: To examine whether circulating vitamin D (25[OH]D) concentrations are associated with insulin resistance (including ethnic differences in insulin resistance) in children

Methods: We carried out a cross-sectional study of 4,650 UK primary school children predominantly of South Asian, black African Caribbean and white European ethnic origins, aged 9-10 years. Children provided fasting blood samples for measurement of circulating 25(OH)D concentrations, insulin, glucose and blood lipids. Anthropometric measurements were made and information on ethnicity and socioeconomic status collected.

Results: Lower average circulating concentrations of 25(OH)D were observed in girls, children of lower socioeconomic status and those with higher fat mass levels, South Asians and black African Caribbeans (throughout the year). In analyses adjusted for age, sex, month, ethnic group and school, inverse associations were present between circulating 25(OH)D and fasting insulin (-0.38%, 95% CI -0.49%, -0.27%), HOMA insulin resistance (-0.39%, 95% CI -0.50%, -0.28%) and fasting glucose (-0.03%, 95% CI -0.05% -0.02%) per nmol/L increase in 25(OH)D. The associations remained after additional adjustments for Fat Mass Index and socioeconomic status. Higher fasting insulin and HOMA insulin resistance among South Asian and black African Caribbean children were reduced by 40-45% after adjustment for circulating 25(OH)D.

Conclusion: Robust randomised placebo-controlled trials are needed to investigate whether increasing circulating 25(OH)D is beneficial for early type 2 diabetes prevention, particularly in children who are vitamin D deficient.

**31. Mr Nick Eckersley**

A measurement of longitudinal neutralising antibody response against pseudovirus spike-protein in serum from SARS-CoV-2 PCR positive patients.

*Eckersley, N., Clark, D., Groppelli, E., Davies, B., Kirwan, D., Augustin, Y., Cusinato, M., Temperton, N., Mayora Neto, M., Monaghan, I., Hadcocks, L., Krishna, S., Planche, T., Staines, H.*

As of 25th November 2022, SARS-CoV-2, the virus responsible for COVID-19, has caused approximately 212,000 deaths in the UK alone and can affect people of all ages. Understanding how the antibody response evolves over time to viral infection is vital in driving the development of new therapeutics, diagnostics and vaccines. Therefore, the purpose of this study was to measure the neutralising capacity of serum from patients previously confirmed as SARS-CoV-2 positive by PCR swab. This was achieved through a pseudovirus neutralisation assay to determine the ability for SARS-CoV-2 specific antibodies, to neutralise the interaction between viral spike protein and human embryonic kidney cells (HEK293T) bearing the ACE-2 receptor and transmembrane serine protease 2 (TMPRSS2).

In total, 1,349 serum samples from 242 PCR positive SARS-CoV-2 patients were obtained sequentially. The samples were screened using a pseudovirus neutralisation assay to determine the neutralising ability of specific antibodies against SARS-CoV-2 Spike. Serum samples which were confirmed to be neutralising (reducing viral transduction by at least 80%, termed pseudovirus neutralisation titre 80%, pVNT80) underwent a further dilution series to determine the lowest titre at which patient serum successfully reached pVNT80. Specificity of the assay was determined using pre-pandemic serum samples. Finally, patients were also categorised into symptom severity scores based on oxygen dependency to determine the effect on antibody neutralisation.

The pseudovirus assay had the greatest sensitivity at 31-60 days post-PCR swab (97.3%). The specificity from 403 pre-pandemic serum samples was 97.8%. For symptom analysis, neutralisation against pseudovirus spike remained consistently higher for patients defined as oxygen dependent compared to those that required no supplemental oxygen. Sub-division by symptom severity showed a significant difference between asymptomatic/mild symptoms and intubated ventilation ($P<0.0001$).

The pseudovirus system is a highly sensitive and specific method for detecting antibody neutralisation to SARS-CoV-2 spike protein for at least 90 days post-PCR swab. Interestingly, patients with the highest levels of symptom severity had stronger antibody neutralisation compared to asymptomatic and mild symptom patients. The data presented here are from a hospital cohort from natural infection, so may not be representative of the wider population or vaccinees.

**32. Mr Felix Effah**

In Vitro High-Throughput Toxicological Assessment of E-Cigarette Flavors in Human Bronchial Epithelial Cells and the role of TRPA1 in Cinnamon Flavor-Induced Toxicity

*Felix Effah, Benjamin Taiwo, Deborah Baines, Alexis Bailey, Tim Marczylo*

Electronic cigarettes (ECs) are considered a less hazardous alternative to tobacco smoking but are not harmless. Growing concerns about the safety profiles of flavors in e-liquids underpin the need for this study. Here, we screened 54 nicotine-free flavored e-liquids (across 15 flavor categories) across the 3-point concentration range (0.25%, 0.5%, and 1% v/v) in a high-throughput fashion in human bronchial epithelial (HBEC-3KT) submerged cultures to identify 'toxic hits' using in vitro endpoint assays comprising cell count, cell viability, and lactate dehydrogenase (LDH). We observed significant, dose-dependent toxic effects only with cinnamon, vanilla tobacco, and hazelnut e-liquids compared to media-only control and PG/VG vehicle. Hence, we further analyzed the toxic hits for their effects on HBEC-3KT proliferation, mitochondrial health, and oxidative stress. A significant decrease in cell proliferation after 36h was observed for each toxic hit compared to media-only and PG/VG controls. Hazelnut (at all concentrations) and vanilla tobacco (1%) increased

cytoplasmic reactive oxygen species (ROS) generation compared to media-only and PG/VG controls. Conversely, all three flavors at 0.5% and 1% significantly decreased mitochondrial membrane potential (MMP) compared to PG/VG and media-only controls. We hypothesized that the cytotoxic effects of cinnamon flavor in e-liquids might be mediated via the transient protein receptor ankyrin subtype 1 (TRPA1); however, TRPA1 antagonist AP-18 (10 ?M) did not mitigate these effects, and cinnamon significantly increased TRPA1 transcript levels. Therefore, pathways that mediate cinnamon's cytotoxicity warrant further investigations. This study could inform public health authorities on the risk assessment following exposure to EC flavor ingredients.

**33. Miss Rawan Elkalaawy**

The value of mid-gestational uterine artery doppler assessment after routine first trimester pre-eclampsia screening

*Meroni, A., Mascherpa, M., Minopoli, M., Lambton, B., Frick, A., Thilaganathan B., Elkalaawy, R*

Objectives: To evaluate whether mid-gestational uterine artery Doppler (UtAD) assessment in women who have undergone the first trimester combined pre-eclampsia screening further modifies the risk of small-for-gestational-age at birth (SGA), hypertensive disorders of pregnancy (HDP) and stillbirth.

Methods: A retrospective cohort study was conducted between May 2019 and January 2022. A total of 7793 women with singleton pregnancies underwent first-trimester screening for preeclampsia using the Fetal Medicine Foundation (FMF) algorithm. All women underwent UtAD Pulsatility Index (PI) assessment at the mid-gestation anomaly scan. Pregnancies were divided into four distinct groups: patients at high risk in both trimesters (H1H2), at high risk in the first but not the second trimester (H1L2), low risk in the first but high risk in the second trimester (L1H2), and low risk in both trimesters (L1L2). The following pregnancy outcomes were assessed: SGA, HDP and stillbirth.

Results: 600 women (7.7%) were designated as high risk in the first trimester and 620 (7.9%) classified as high risk at mid-gestation. Risk groups were as follows: 161 H1H2 (2.1%), 439 H1L2 (5.6%), 459 L1H2 (5.9%) and 6734 L1L2 (86.4%). The prevalence of preterm preeclampsia decreased consistently with risk assessments from 13.7% in H1H2 to 0.2% in L1L2 groups (all $p<0.01$). Preterm preeclampsia was more prevalent in high risk women with normal mid gestational UtAD PI (H1L2, 4.4%) than in women classified as low risk in the first trimester (0.4%, $p<0.0001$). Similarly, the prevalence of preterm preeclampsia in low risk women with high mid gestational UtAD PI (L1H2, 3.4%) was significantly lower than in women classified as high risk in the first trimester (7.0%, $p=0.0076$). The prevalence for SGA and HDP followed the same trends as for preterm preeclampsia.

Conclusions: Preeclampsia risk in women who have had first trimester preeclampsia screening using the FMF combined algorithm may be further stratified through routine UtAD scan. Pregnancy care should not be de-escalated on the basis of low mid-gestational UtAD impedance in patients that were classified as high risk in the first trimester. In contrast, escalation of care may be justified in low-risk women with high mid-gestational UtAD resistance.

**34. Miss Meryemnur Enver**

Retrospective Analysis of Factors Associated with a Successful Induction of Labour in Twin Pregnancies in a Large London Teaching Hospital Between 2016 and 2020

*Author: Enver, M*

*Supervisors: Khalil, A and Prasad. S*

Objective: To identify factors associated with a successful induction of labour (IOL) in twin pregnancies, by considering both maternal and foetal parameters during the prepartum, intrapartum and postpartum stages of pregnancy.

Design: A retrospective cohort study of 102 induced twin pregnancies during the study periods 2016 to 2020.

Method: Data was extracted from an excel spreadsheet from viewpoint software and E3 EuroKing database for maternal demographics, as well as antepartum, intrapartum and neonatal outcomes.

The following predicting factors of vaginal delivery during induction were collected and analysed; age, BMI, ethnic origin, parity, conception, chorionicity, Bishop's score, method of induction, reason for induction, length of labour, type of analgesia, post-partum haemorrhage (PPH) and choriamniotis. Foetal parameters included gestational age, mode of delivery, birth weight, gender, Apgar score, and admission to NICU.

Results: Women that had a combination of induction methods were associated with the highest rate of unsuccessful IOL, followed by prostaglandin administration alone. When considering the indications for induction, pre-eclampsia, followed by preterm rupture of membranes, had the highest association with an unsuccessful IOL.

A greater proportion of dichorionic pregnancies underwent an emergency caesarean section due to an unsuccessful IOL, compared to monochorionic pregnancies.

Parous women had a higher success rate of IOL of 86%, compared to 53.3% in non-parous women. Also, women that underwent fertility treatment had a lower successful IOL rate of 58.8% compared to 74.1% of those that did not.

Analysing the Apgar scores, we found that 71.4% of all babies with an Apgar score of <7 was the second baby to be delivered, of which only 20% had a successful IOL. Furthermore, 95% of mothers with a Bishop's score of 6 or more had a successful IOL, in comparison to 64.9% of those with a Bishop's score below 6.

Looking at intrapartum complications, we found that 71.4% of induced women with chorioamnionitis required an emergency caesarean section, in comparison to 25.5% of those who did not.

Conclusion: This study has shown the following factors to be contributors to the success of IOL: method of induction, indication for induction, mother's parity status, Apgar and Bishop scores, labour time, chorionicity and the presence of chorioamnionitis.

**35. Miss Stephanie Fang**

Quantification of Oligodendrocytes (OLs) and Oligodendrocyte Precursor cells (OPCs) in the ageing human brain using CD140A and SOX10

*S Fang, J Jeevahan [in Cell Path – she did the Sox10], LR Bridges, AH Hainsworth*

Background: Oligodendrocyte Precursor Cells (OPCs) are the most prominent proliferative cells of the central nervous system, accounting for 5-10% of the total cells in the brain. OPCs' main function is to provide a pool of progenitors that mature into oligodendrocytes (OLs). Recent research suggests various functions of OPCs other than OL differentiation and remyelination, such as modulating neighbouring astrocytes and neurone, or contributing to innate immune responses.

Aims: The main objectives were to identify and quantify the number of OPCs and a combination of OPCs and OLs in white matter (WM) in human brain tissue and in individuals with and without cerebral small vessel disease (CSVD).

Method: Manual immunohistochemistry was performed to identify OPCs using CD140A antibodies. Automated immunohistochemistry was performed in the St George's Hospital Cellular Pathology Lab to identify OPCs & OLs using SOX-10 antibodies.

For SOX-10, 13 brain donors were used; for CD140A, 19 brain donors were used. GFAP and Rabbit anti-sheep IgG polyclonal antibody (RAS) provided positive and negative controls respectively. Staining was followed by microscopy and digital image analysis using the National Institute of Health ImageJ software to produce manual and automated OPC counts and automated total OL and OPC counts. Lastly, a Mann Whitney U test and Spearman's rho were performed.

Results: The extent of CD140A labelling for OPCs was not significantly correlated with age in WM (p=0.352). Amongst individuals aged ? 70, WM OPC density was significantly decreased in brains with CSVD compared to brains without CSVD according to the automated count (p=0.016); however, this significant difference was not observed using the automated count (p=0.067). The total population of OPCs and OLs remained relatively stable in patients with and without CVSD despite the visually significant difference in the decrease in OPCs according to the box and whisker plots.

Conclusion: Overall, the trend in our data indicated that OPC density decrease with age but not significantly. This may be due to the age-related decrease in OPC proliferation rate. CSVD was associated with a significant decrease in OPC counts which may be indicative of dysfunctional endothelial cell OPC signalling that was linked to OPC death.

**36. Dr Sarah Ford**

Audit of high sensitivity cardiac troponin requesting patterns in routine clinical use.

*Ford,S., Krishnanandan, S., Collinson, P*

Introduction: Routine measurement of troponin by a high sensitivity method (hs-cTn) has been in routine use in the UK for 12 years and accelerated diagnosis recommended since 2014. We conducted an audit of requesting patterns against current protocols.

Methods: The current protocol uses a single test on admission with patients considered for discharge if low clinical risk and hs-cTnT is<3ng/L. Patients with hs-cTnT>50ng/L are admitted. Patients with an initial troponin 14-50ng/L have a repeat 3hour test - if the repeat test is<14ng/L with delta(3h sample-0h sample)<=7 and low-risk, patients are discharged. Patients ranging 14-50ng/L with delta<=7ng/L are further assessed; delta>7ng/L are admitted.

All troponin results between August-November 2021 from the emergency department(ED) were extracted from the laboratory information system. Data was transferred to a relational database(Access) for analysis. Non-parametric statistics were analysed with the AnalyseIt add-in for Excel. Results were divided into single or serial tests/patient episode.

Results: Data was obtained from 7352 requests on 6980 patients. 306 patients had multiple attendances. There were 4869 single requests from 4593 patients, 996(20.5%)<3ng/L, 2664(54.7%)3-50ng/L, 270(5.5%)>50ng/L. Hence 26.0% of patients could be discharged or admitted using a single troponin. Serial testing occurred in 2483 episodes in 2387 patients. 99(2.7%) had both cTnT values 3ng/L, 282(11.4%) of the initial values were>50ng/L. 1260 had initial values 3-14ng/l(50.7%), with delta<=7ng/L in 1248(50.3%). There was delta<=7ng/L in 809/873 of those 14-50ng/L. Even in patients with a significantly abnormal cTnT(>200ng/L), a raised delta was seen in only 86/282.

Conclusion: Use of the current protocol allowed identification of low-risk in 31.4% patient episodes. Troponin requesting patterns in clinical practice differ significantly from recommendations, reflecting the use of troponin as a catch-all test for possible cardiac damage in patients presenting with other clinical conditions where a single test is regarded sufficient. Lack of repeat testing for values between 14-50ng/L was surprising and requires further investigation.

**37. Dr Sarah Ford**

Feasibility Of Implementing A 0-2 Troponin Algorithm

*Ford,S., Krishnanandan, S., Collinson, P*

Introduction. Recent guidelines have recommended rapid diagnosis based on repeat sampling at 2 hours from admission. We investigated the feasibility and diagnostic equivalence of repeat measurement at 2 hours by comparing the diagnostic classification achieved by measurement at 0 and 2 hours with a delta value of <=3 between samples to measurement at 0 and 3 hours and a delta of <=7ng/L between samples.

Methods. From August to November 2021 all patients with chest pain where a diagnosis of acute coronary syndrome (ACS) was considered had a diagnostic protocol of measurement of cardiac troponin T (cTnT) on admission and at 2 and 3 hours from admission. Requests and results f were extracted from the laboratory information system including date and time of result. Data was transferred to a relational database (Access, Microsoft corp) for analysis. Non-parametric statistics were used throughout using the Analyse It.(www.analyse-it.com) add in for Excel. Cardiac troponin T (cTnT) was measured by the Roche high sensitivity cardiac troponin T assay hs-cTnT (Roche diagnostics), range 3 - 10,000ng/L, 10% CV 13ng/L, 99th percentile 14 ng/L.

Results. 728 sets of serial samples where obtained on 711 patients, 40.1% female median age 61.8 years,(interquartile range 50.6-75). Comparison of classification showed agreement between the 2 hour and 3 hour delta in 593 cases (558 rule out, 35 rule in) and disagreement in 43. There where 37 cases that would have required further investigation, either by repeat sampling or admission. In 6 cases a positive 3 hour delta occurred with a 2 hour delta of 3 or less. 4 had values exceeding the 99th percentile on the admission sample so would have been retained for further investigation. The remaining 2 patients had co-existing clinical conditions that required further investigation.

Conclusion. The routine use of serial sampling at admission and 2 hours was clinically safe and resulted in the same clinical decisions in the context of the busy ED environment for the population served by the hospital. However, this was at the expense of requiring further testing of some patients. The optimum strategy in this group remains to be determined.

**38. Miss Elizabeth Forrester**

Possible role for CGRP in Dapagliflozin mediated relaxation

*Forrester E, Durrani S and Greenwood I*

Introduction: Sodium dependent glucose transporter 2 (SGLT2 or SLC5A2) inhibitors improve glycaemic control in diabetic patients, by preventing glucose reabsorption from the renal proximal tubule. In addition, SGLT2 inhibitors offer a cardioprotective benefit in diabetic and non-diabetic patients. Whilst the mechanism is unknown there is evidence that the ability of SGLT2 inhibitors to lower peripheral resistance and blood pressure is unlikely to be attributed to increased diuresis alone. We aimed to ascertain whether dapagliflozin relaxed rat arteries and whether the potent vasodilator, calcitonin gene-related peptide (CGRP) was involved.

Experimental approach: The effects of dapagliflozin were determined via Wire-Myography on pre-contracted renal and 2nd order mesenteric arteries from male Wistar rats, in the presence of several CGRP, TRPV1 and potassium channel blockers. Expression of SLC5 transporter in mesenteric arteries were determined by RT-qPCR and immunocytochemistry. In-silico simulations of drug binding to the channel were performed.

Results: Slc5a1 and Slc5a2 (SGLT1 and SGLT2) were not expressed in mesenteric arteries, yet the SGLT2 inhibitor dapagliflozin relaxed pre-contracted mesenteric from male rats by ~67% (N=8). The relaxation evoked by 30uM Dapagliflozin was significantly attenuated upon pre-incubation with 1µmol-L-1 CGRP antagonist, BIBN ($P<0.0001$). Selective pharmacological inhibition of the TRPV1 receptor using 1µmol-L-1 AMG 517 and wipe-out of all neuronal CGRP by 2-hour capsaicin incubation significantly attenuated the relaxation to dapagliflozin

in mesenteric arteries by 32.3% and 28.7% respectively (P<0.0001). Pre-application with the pan-Kv7 channel blocker linopirdine (10μmol-L-1) impaired relaxations produced by dapagliflozin and exogenous CGRP. Using in-silico docking dapagliflozin is predicted to bind to TRPV1.

Conclusions: This study is the first to demonstrate that SGLT2 inhibitors evoke vasorelaxation in mesenteric arteries through interaction of TRPV1 and CGRP release.

**39. Miss Anne-Marie Gabrawi**

The use of cardiovascular mechanisms of death in the Office of National Statistics mortality statistics

*Anne-Marie Gabrawi, Mary N Sheppard, Joseph Westaby*

The office for national statistics (ONS) holds a record of all causes of death in England and Wales according to the International Classification of Diseases 10th Revision. In some cases, a mechanism of death, such as arrhythmia, may be given. We aimed to quantify the proportion of cardiovascular deaths being coded as a mechanism of death from the ONS.

We analysed the ONS records from 2013 – 2021, inclusive. There were 4,852,897 deaths overall, of which, 836,741 (17.2%) were cardiovascular. Of these, 103,160 (12.3%) were labelled as mechanisms and 35,784 (4.3%) were non-specific causes. The most common mechanisms being used were atrial fibrillation and flutter, unspecified (52,321 (6.25%)) congestive heart failure (31,248 (3.7%)) and heart failure, unspecified (12, 374 (1.5%)). The most common non-specific codes being used were myocardial degeneration (12,192 (1.5%)), unascertained deaths (10,605 (1.3%)) and cardiomegaly (6,573 (0.8%)).

Mechanisms of death do not aid in the screening blood relatives for inherited cardiac conditions. Causes should be listed as an underlying disease process such as ischaemic heart disease (IHD) or hypertrophic cardiomyopathy. This enables screening to be focussed on specific diseases. The use of a mechanism of death as opposed to a specific disease should prompt a referral for autopsy.

**40. Dr Lucy Goldsmith**

The impact of social media and covid-19 misinformation on migrants and racially minoritised populations: a systematic review

*Goldsmith LP, Rowland-Pomp M, Hanson K, Deal A, Crawshaw AF, Hayward SE, Knights F, Carter J, Ahmad A, Razai M, Vandrevala T, Hargreaves S.*

Objective: Migrants and ethnic minority groups have been disproportionately impacted by COVID-19 and have lower levels of vaccine uptake in some contexts. We aimed to determine the extent and nature of social media use in migrant and ethnic minority communities for COVID-19 information, and to ascertain the implications for preventative health measures including vaccination uptake and intent.

Design: We conducted a systematic review of published and grey literature following the PRISMA guidelines. We searched databases including Embase, Web of Science, PubMed NIH, CINAHL, facilitated through the WHO Global Research on COVID-19 database from 31/12/2019 to 9/6/2021.

Eligibility criteria for study inclusion: We included research reporting the use of social media by migrants and/or ethnic minority groups to find information about COVID-19.

Data extraction: We extracted data on key outcomes, study design, country, population under study, and sample size.

Results: 1849 unique records were screened, and 21 data sources included including populations in the UK, US, China, Jordan Qatar, and Turkey. We found evidence of consistent use of a range of social media platforms for

COVID-19 information in some migrant and ethnic minority populations (including WeChat, Facebook, WhatsApp, Instagram, Twitter, YouTube), which may stem from difficulty in accessing COVID-19 information in their native languages or from trusted sources. Some evidence suggested circulating misinformation and social media use may be associated with lower participation in preventative health measures, including vaccine intent and uptake, findings which are likely relevant to multiple population groups.

Conclusions: Social media platforms are an important source of information about COVID-19 for some migrant and ethnic minority populations. Urgent actions and further research are now needed to better understand effective approaches to tackling circulating misinformation, and to seize on opportunities to better use social media platforms to support public health communication and improve vaccine uptake.

Registration: This study has been registered with PROSPERO;(CRD42021259190).

**41. Dr Davina Hensman Moss**

HTT repeat instability in family trios in the 100,000 Genomes Project

*Davina Hensman Moss*(1,2,3), Anupriya Dalmia*(4), Valentina Galassi Deforie(2), Kristina Ibanez(4), Sarah J Tabrizi(2), Nayana Lahiri(1, 3), Henry Houlden(2), Peter Holmans(5), Lesley Jones(5), Arianna Tucci(4)*

*1 Molecular and Clinical Sciences Researc*

Background: The HTT-CAG repeat is intergenerationally unstable, driving both new cases of Huntington's disease (HD) in previously unaffected families and genetic anticipation. Aims: To characterize the intergenerational patterns of HTT-CAG repeat instability in a non-HD cohort, and identify genetic factors influencing this. Through this we aim to better quantify the risk of a parent who carries an intermediate HTT-CAG repeat passing on an expanded allele to their children, improving the information that can be provided in genetic counselling.

Methods/Techniques: The UK 100,000 Genomes Project has sequenced 100,000 whole genomes from 85,000 subjects affected by rare disease or cancer. We deploy a 3-step approach: 1) characterize the frequencies of intermediate, normal and expanded HTT-CAG repeat alleles within the 100,000 genomes cohort, 2) identify parent-offspring trios, and quantify repeat instability by studying transmission from parents to offspring, 3) look at the effect of genetic factors, including variants in DNA damage repair genes on intergenerational repeat instability.

Results/Outcome: 10,127 mother-father-proband trios were selected for whom we have complete clinical and WGS data. 6.1% of the parent population carries an intermediate allele, consistent with previous studies. Of 10,127 trios, 154 (1.5%) carry instability in STR transmission from parent to offspring. The CAG repeats have been phased relative to surrounding SNPs enabling us to determine parent of origin for expansion/contractions: both expansions and contractions occur on both paternal and maternal alleles. Rare variants of large effect have been identified in DNA repair genes previously associated with HD age-at-onset and progression in families with intergenerational CAG repeat changes.

**42. Miss Savini Hewage**

An Audit of Establishment of Feeds in Preterm Neonates at SGH NNU

*Hewage,S., Aziz,N.*

Aims

•To assess whether full feeds (150ml/kg/day) were established within the recommended targets set by the St George's Hospital Neonatal Unit (SGH NNU), in infants less than 34 weeks.

•To explore the reasons why neonates were not progressing in their feeds.

•To explore the link between establishing feeds during the first 5 days of life and necrotising enterocolitis (NEC).

Methods: This study examined the data of 35 premature babies born at SGH between April 2020 and February 2021. Using Badgernet (an online database with detailed notes on neonates) as well as the SGH clinical notes accessed using PowerChart on iClip multiple parameters were recorded. These included weeks of gestation (ranging from 23 weeks – 27 weeks in this sample), day of life neonates were started on milk, type of milk started and issues with progression of feeds. Data collected was stored on an encrypted USB and deleted following the study to comply with Data Protection regulations.

Results

•11.4% of neonates met the SGH NICU feeding guidelines (establishing full feeds of 150ml/kg/day before 8 days of life)

•Over half of the neonates established the target within 16 days

•49% of neonates were started on milk on day 1 of life

•Reasons for neonates not progressing with their feeds were abdominal distension (potential sign of NEC), infection, and bilious aspirates

•Only 1 neonate presented with NEC despite 8 other babies having clinical suspicion of NEC

•All babies were started on human milk with the majority started on maternally expressed breastmilk.

Conclusion: This audit has shown that most infants under 34 weeks on SGH NICU are not meeting the guidelines for establishing full feeds and in commencing feeds on day 1 of life. This is due to a variety of reasons in particular suspected NEC, infection and bilious aspirates. These factors could be incorporated into early warning scores to allow more consistent decision making when stopping feeds. Most neonates were started on maternal expressed breast milk which should continue to be encouraged. Results of this study have been presented to the NICU team and will be used as baseline data for quality improvement initiatives.

**43. Dr Rory Higgins**

**44. Miss Holly Hughes**

Development of a FRET-based sensor of glutamate transport

*Hughes H 1, Tran O 1, Puhl H 2, Nguyen T 2, Vogel S 2, Carter T 1 and Török K 1*

Glutamate is the main excitatory neurotransmitter in the brain, with key roles in learning, memory and synaptic plasticity. Excess glutamate in the synaptic cleft must be swiftly cleared away to prevent excitotoxicity, associated with neurological disease. Excitatory amino acid transporter (EAAT) 2 is estimated to account for over 90% of glutamate uptake and undergoes significant conformational changes as it transitions from an outward-facing to an inward-facing state during glutamate transport. Such conformational changes suggest the transporter could be an exciting novel candidate for Förster Resonance Energy Transfer (FRET) studies to investigate its function in health and disease.

In the present research, we are developing genetically-encoded FRET-based sensors which take advantage of conformational changes at the monomeric and trimeric levels of EAAT2. Properties of fluorescent protein (FP) FRET pairs were compared using FPbase, and distances between putative FP insertion sites in EAAT2 were measured in the crystal structures of homologous transporters, in the outward and inward-facing conformations. EAAT2-FP constructs designed accordingly were synthesised by Gibson assembly and

transfected into HEK293T cells. Plasma membrane expression of the EAAT2-FP constructs was determined by confocal microscopy, and glutamate transporter activity was investigated using a novel live-cell imaging assay with an intracellular version of the ultrafast glutamate sensor iGluu.

FP insertion sites located near the C-terminus of EAAT2 on different sub-units are predicted to move further apart by >30 Å when glutamate moves into the cell. The mNeonGreen/mCherry FRET pair was used to label the E512-D513 site and the resulting constructs showed comparable levels of plasma membrane expression to wild-type EAAT2 (89.7% of cells on average for wild-type EAAT2 and up to 1.1% difference for EAAT2 mNeonGreen/mCherry E512-D513). The high levels of plasma membrane expression indicated that the transporter activity is likely to be retained, as reflected in live-cell imaging data showing a similar decrease in glutamate indicator fluorescence for the wild-type and FP-containing EAAT2 (wild-type EAAT2 t1/2 33.2 s and dF/F0 0.285; EAAT2 mCherry E512-D513 t1/2 50.7 s and dF/F0 0.270). When glutamate was added to cells co-expressing EAAT2 mNeonGreen/mCherry E512-D513, there was decreased fluorescence lifetime, consistent with the predicted decrease in FRET efficiency.

**45. Mr George Hunt**

Do urine measurements of luteinising hormone (LH) and follicle stimulating hormone (FSH) provide a good enough proxy for serum levels in polycystic ovary syndrome (PCOS)?

*George Hunt, Dr Sarah Johnson, Sarah Weddell, Dr Irina Chis Ster, Dr Gul Bano, Dr Suman Rice*

Background: Polycystic Ovary Syndrome (PCOS) is a common endocrine pathology characterised by polycystic ovaries, ovulatory irregularities & hyperandrogenism (Fauser et al., 2004; Bozdag et al., 2016). Current research tends to focus on serum LH and FSH levels in PCOS and non-PCOS populations (Davis, Fletcher and Chapman, 2012; Zhou et al., 2020; Karimi et al., 2021; Cai et al., 2022). Acquiring serum samples can be laborious and time consuming, therefore, if urine measurements could be used as a proxy for serum levels, this could potentially facilitate diagnosis/monitoring of PCOS.

Aims: To explore the potential associations between urine and serum LH and FSH measurements in PCOS women. To investigate associations between BMI, vitamin D levels and status, waist:hip ratio, homeostatic model assessment 2 (HOMA2), insulin resistance status and free androgen index (FAI) with urine and serum LH and FSH in the same population.

Methods: Data were collected between 2018 and 2020. Investigations from 56 women with Rotterdam Criteria diagnosed PCOS included fasting glucose and insulin, and a range of hormones – testosterone, sex hormone binding globulin (SHBG), LH, FSH and, vitamin D. Urine samples measured LH, FSH and, creatinine.

Results and conclusions: All correlations and associations between urinary (both corrected and non-corrected) and serum LH and FSH were statistically significant (correlations $p<0.05$, associations $p<0.001$) with correlations ranging from a moderate to very strong correlation. There was a significant univariate association between corrected urinary LH against both BMI ($p=<0.001$) and HOMA2 ($p=0.003$), urinary LH against BMI ($p=0.011$) and urinary FSH against vitamin D levels ($p=0.013$) and status ($p=0.047$). The only significant variable in a multivariable regression model was corrected urinary LH against BMI when adjusted for all other covariates ($p=0.005$). These findings show that corrected urinary LH and FSH can be used as a proxy for serum measurements in women with PCOS; which may have future implications to improve monitoring of PCOS in settings such as general practice.

**46. Miss Naomi Ike**

Implementing and managing nurse led reviews of patient outcomes at 3 and 6 months following mechanical thrombectomy for acute ischaemic stroke

*N. Ike, J. Corns , G. Cluckie, L. Zhang, S. Hassan, A. Ogungbemi, B. Clarke*

**47. Ms Bryony Ishihara**

Lesion characteristics on MRI following radiofrequency thalamotomy for tremor

*Bryony Ishihara., Erlick Pereira., Michael Hart*

Objectives: Unilateral radiofrequency (RF) thalamotomy is a treatment option for medication-refractory tremor. Our aim was to understand the features of the resultant lesion, their temporal dynamics, and how they vary depending on surgical factors. Using a neuroimaging analysis, we report on the MRI characteristics – including size and location – of the lesions and associated oedema over time and across different MR sequences.

Methods: Post-operative MRI data of 12 patients who underwent unilateral RF thalamotomy for tremor were analysed retrospectively. Lesion volumes were calculated from the manual segmentations of regions of hypointensity (lesion core) and hyperintensity (oedema) on FLAIR, T2, SWI and FGATIR sequences, using FSLeyes. Lesion location was determined after registration of lesions to the MNI standard space.

Results: All 12 patients had clinically meaningful tremor improvement post-operatively. Complications included 2 instances of gait ataxia and 1 instance of transient confusion (3 out of 12 patients). Lesion volumes were larger on FLAIR compared to T2 (mean 622 ± 229 $mm^3$ versus 524 ± 199 $mm^3$, t=-4.64, p=0.002) and lesion features were best demarcated on T2 sequences. Multiple lesions were associated with greater cytotoxic oedema compared with single lesions (T2 mean: 537 ± 112 $mm^3$ versus 302 ± 146 $mm^3$, t=2.75, p=0.028), while size of the necrotic core did not significantly differ (T2 mean: 106 ± 9 $mm^3$ versus 73 ± 40 $mm^3$, t=1.76, p=0.122). Total lesion volume reduced on average by 86% between the first (12 ± 3 days post-surgery) and second (254 ± 131 days post-surgery) scans (T2 mean 606 ± 62 versus 86 ± 51 $mm^3$, t=19.18, p<0.001, n=4), and appeared to stabilise at approximately 6 months after surgery.

Conclusions: Neuroimaging analyses offer potential to study dynamic lesion characteristics following RF thalamotomy. T2-weighted scans are readily suitable for distinguishing between the lesion core and oedema characteristics. Scanning patients in the immediate post-operative period and then at 6 months is clinically relevant for understanding the transient and permanent effects of thalamotomy.

**48. Prof Heather Jarman**

Feasibility of smartphone application use to support recovery in patients discharged from the Emergency Department with uncomplicated back pain

*Murray, E. Wanless, B. McClellan, C. Jarman, H.*

Introduction: Musculoskeletal back pain is a common presentation to Emergency Departments, with prevalence of 4.39% internationally. Clinical guidance on treatment of back pain consistently recommends self-management including monitoring of symptoms and exercise. Emerging evidence suggests smartphone applications can be used effectively in supporting the recovery of patients. The use of self-management apps in the ED is less well explored. We investigated the feasibility of introducing a self-management app (getUBetter©) as part of revised clinical practice guideline on the management of patients discharged from the ED with uncomplicated MSK back pain.

Methods: A retrospective cohort study of patients age 18 and over visiting the ED with uncomplicated musculoskeletal back pain was conducted between July 2021 and January 2022, 2-months after the introduction of the revised pathway. We ascertained the number of patients suitable to use the self-management app and compared this with the number provided with the app on discharge. We conducted a web-based survey of patients and ED clinicians to ascertain their opinions on the use of the app. Frequencies were calculated using descriptive statistics, and free text survey responses were analysed thematically.

Results: Of the 874 patients with uncomplicated back pain, 836 (95.65%) met the inclusion criteria for the app (median age 44, IQR 33-56; female 56.3%). Documentation on provision of the app was found for 141 (16.8%)

patients, of whom 90 went on to use the app (63.8%). Fourteen patients and 15 clinicians responded to the survey, with a mean rating of 4 out of 5 given to the overall usability of the app. Clinicians felt the app gave patients more independence in their recovery.

Discussion and conclusions: The results show that the majority of patients attending our ED with uncomplicated back pain could benefit from a self-management app as part of their recovery. Further work is needed to embed the use of the app within the local clinical guideline.

**49. Prof Heather Jarman**

Diagnosis of carbon monoxide exposure in clinical practice and research: a scoping review

*Babu, A., Moss, P., Reid, S., Jarman, H.*

INTRODUCTION: Carbon-monoxide (CO) is a colourless, odourless gas produced from incomplete combustion of carbon-containing fuels. Measurement of CO levels to diagnose exposure is difficult due to its short half-life. The effects of exposure to CO range from mild symptoms, such as headache, to neurotoxicity and death.

In this scoping review we aimed to establish the existing methods used in clinical practice and research to determine CO exposure and map the diagnostic cut-off values used.

METHOD: We undertook a scoping review to establish methods used in clinical practice and research to measure CO exposure and to determine diagnostic thresholds in each. EMBASE, Medline and CINAHL databases were searched for published articles in English from 2002 onwards using keywords “carbon monoxide”, “poisoning” and “diagnosis”. Two reviewers independently screened published abstracts for inclusion, with a third arbiter where there was lack of agreement between reviewers. Full text papers were then reviewed, and data extracted on methods used to measure CO level, diagnostic cut-off values, and whether CO exposure was from a known or unknown source.

RESULTS: A total of 68 papers were identified meeting the inclusion and exclusion criteria. The most common methods identified for diagnosing CO exposure were measurement of carboxyhaemoglobin (COHb) in whole blood (50.5%) and CO-oximeter spectrophotometrics (20%). Diagnostic values were poorly reported and varied in non-smokers and smokers. Exhaled CO levels using breath analysers (8.2%)?and ambient CO measurement (11.7%) were also documented. Diagnostic threshold values varied between 2-5% in non-smokers and 10-15% in smokers. Several methods are used in clinical practice and research to diagnose CO exposure. There is variation in the cut-off values used to make this diagnosis which is challenging for clinicians and makes comparison of research findings difficult.

**50. Prof Heather Jarman**

Emergency nurses’ preference for tools to identify frailty in major trauma patients: a prospective multi-centre cohort study

*Jarman, H. Crouch, R. Baxter, M. Wang, C. Cole, E.*

Background: Early assessment of frailty is an important factor in guiding frailty-specific care in older major trauma patients. It is recommended this is performed in the Emergency Department (ED) but there are time and clinical challenges to doing this accurately. To increase rates of frailty screening in this group the measurement tool needs to be quick to complete and easy to use. This study aimed to ascertain the preference of nursing staff completing frailty assessment in older major trauma patients in the ED.

Methods: This prospective multi-centre study recruited from five UK Major Trauma Centres between June 2019 and March 2020. Eligible patients were aged 65 or over requiring ‘trauma team activation’ and admitted to hospital. Patients were assessed for frailty by nurses trained to use three different frailty screening tools –

the Clinical Frailty Scale (CFS), the PRISMA-7 tool, and the Trauma Specific Frailty Index (TSFI). Completion rates for each of the tools were calculated and nurses were asked to rate their preference for each of the tools and the reasons for non-completion if relevant.

Results: Data were analysed from 370 patients. Completion rates for each of the tools varied with highest degree of compliance using the CFS (98.9%). TSFI was least likely to be completed with "lack of available information to complete questions" as the most cited reason. Nurses showed a clear preference for the CFS with 57.3% ranking this as first choice (PRISMA-7 32.16%; TSFI 10.54%). Both PRISMA-7 and CFS were both rated highly as 'extremely easy to complete' (PRISMA-7 58.5%, CFS 59.61%).

Conclusion: User acceptability is an important consideration in the selection of a frailty measurement tool for use in major trauma patients. Our study shows the Clinical Frailty Scale has high rates of completion and acceptability and can be implemented in practice for assessment of frailty in major trauma.

**51. Dr Nishani Jayasooriya**

Time to diagnosis and the impact of delayed diagnosis on clinical outcomes in inflammatory bowel diseases: a systematic review and meta-analysis

*Jayasooriya N, Baillie S, Blackwell J, Bottle A, Petersen I, Creese H, Saxena S, Pollok R.C, POP-IBD study group*

AIMS: The impact of diagnostic delay on the clinical course of inflammatory bowel diseases (IBD) remain uncertain. We performed a systematic review of time to diagnosis and the impact of delayed diagnosis on clinical outcomes in Crohn's disease (CD) and ulcerative colitis (UC).

METHODS: We searched EMBASE and Medline, inception-to-30.09.2022, for studies reporting diagnostic interval, from symptom onset to IBD diagnosis. We calculated the median, inter-quartile range (IQR), and pooled weighted median, of median diagnostic intervals of eligible studies. We defined delayed diagnosis as individuals above the 75th centile of the longest time to diagnosis in each study. Using random-effects meta-analysis, we pooled odds ratios (ORs) with 95% confidence intervals (CI) for studies reporting clinical outcomes, according to delayed diagnosis.

RESULTS: 101 studies representing 112,194 IBD patients (CD=59,359;UC=52,835) met inclusion criteria. The median of median times to diagnosis was 8.0 (IQR:5.0-15.2) and 3.7 months (IQR:2.0-6.7) in CD and UC, respectively. In high-income-countries, this was 6.2 (IQR:5.0-12.3) and 3.2 months (IQR:2.2-5.3), compared with 11.7 (IQR:8.3-18.0) and 7.8 months (IQR:5.2-21.8) in low-middle-income-countries, for CD and UC, respectively. The pooled weighted median was 7.0 (95%CI:3.0-26.4) and 4.6 (95%CI:1.0-96.0) months, for CD and UC, respectively. Eleven studies were included in the meta-analysis, representing 6,164 patients (CD=4,858;UC=1,306). In CD, delayed diagnosis was associated with a higher likelihood of stricturing (OR=1.88;CI:1.35-2.62), penetrating disease (OR=1.64;CI:1.21-2.20), and intestinal surgery (OR=2.24; CI:1.57-3.19). In UC, delayed diagnosis was associated with a four-fold likelihood of colectomy (OR=4.13;CI:1.04-16.40).

CONCLUSION: Delayed diagnosis is associated with disease progression in CD, and intestinal surgery in both CD and UC. Strategies are needed to achieve earlier diagnosis of IBD.

**52. Dr Nishani Jayasooriya**

Antidepressant medication use in Inflammatory Bowel Disease: a nationally representative population-based study

*Jayasooriya N, Blackwell J, Saxena S, Bottle A, Petersen I, Creese H, Hotopf M, Pollok R.C, POP-IBD study group*

Background: Despite high rates of depression and anxiety, little is known about the use of antidepressants amongst individuals diagnosed with inflammatory bowel disease (IBD).

Aims: To evaluate temporal trends in the use of antidepressants; rates of antidepressant initiation and adherence of antidepressant use to international guidelines amongst individuals with IBD.

Methods: This is a study of 14,525 incident IBD cases from 2004 to 2016 compared with 58,027 controls matched 1:4 for age and sex from the Clinical Practice Research Datalink. After excluding tricyclic antidepressants, we performed a Cox regression analysis to determine the risk associated with antidepressant use and logistic regression analysis to determine risk associated with antidepressant undertreatment.

Results: Antidepressant use amongst individuals with IBD increased by 51% during the 12-year study period, who were 34% more likely to initiate antidepressants in the year after IBD diagnosis compared with controls (aHR:1.34, 95% CI 1.21-1.49). In those with IBD starting antidepressants, 67% received treatment lasting less than the duration recommended in international guidelines, of which 34% were treated for 1 month or less.

18–24-year-olds were twice as likely to discontinue treatment within 1 month compared with those aged 40-60 years (aHR:2.03, 95% CI 1.40-2.95). Socioeconomic deprivation was also associated with early treatment discontinuation (aHR:1.40, 95% CI 1.07-1.83).

Conclusions: In the year following IBD diagnosis individuals are significantly more likely to start antidepressants compared with controls, but treatment duration fell short of recommendations in the majority. Better integration of services may benefit individuals with IBD and psychiatric comorbidity.

**53. Miss Yiwen Jin**

The Importance of the SLC44A2 rs2288904 Polymorphism in Platelet-Leukocyte Interactions

*Yiwen Jin1, Laura Mereweather2, James TB Crawley2 and Isabelle I Salles-Crawley1,2*

Haemostasis is a delicate balance between bleeding and thrombosis, which prevents blood loss from intact and injured vessels, and enables tissue repair. Platelets are recruited to the site of injury via collagen-bound von Willebrand factor (VWF) and form a clot which is stabilised with fibrin to stop and prevent further bleeding. Platelets fulfil their haemostatic capacity via adhesion, activation, and aggregation, which are triggered upon tissue injury. These processes stimulate the coagulation pathway and mediate haemostasis. Interactions between platelets and neutrophils are essential for haemostasis but also contribute to pathological thrombus formations such as deep vein thrombosis (DVT).

A recent genome-wide association study with over 60,000 human subjects showed that the gene SLC44A2 was associated with a ~20% increased risk of thrombosis. A single nucleotide polymorphism (SNP) in SLC44A2 called rs2288904 (G/A), present in ~22% of the population, causes a missense mutation R154Q, which was found to provide protection against venous thrombosis. We recently showed that Q154/Q154 neutrophils have diminished ability to interact with VWF-primed platelets providing a mechanistic link between SLC44A2 and DVT. T-cells can also interact with VWF-primed platelets via ?IIb?3; however, this interaction has not been fully investigated. In our study, we hypothesise that primed platelet/T-cells interactions are also SLC44A2-dependent and that the rs2288904 SNP influences the binding of T-cells to primed platelets. We genotyped 26 healthy volunteers to identify individuals carrying the protective allele at the rs2288904 SLC44A2 locus. Nearly half of the individuals (11/26) were heterozygote for the rs2288904-A minor allele, and one homozygote for the SNP was identified. Using flow cytometry, we confirmed the high expression of SLC44A2 in neutrophils

compared to T-cells, while no expression was detected on platelets. Using microfluidic flow channels, neutrophils and T-cells harbouring the R154Q substitution interacted less with primed platelets. We can therefore confirm that neutrophils from individuals' homozygote for the rs2288904-A protective allele interact less with primed platelets, but the diminished interactions of T-cells will need to be further assessed. Indeed, our results suggest that the number of T-cell interactions with primed platelets in individuals carrying the major risk allele was much less than that of neutrophils.

**54. Miss Hannah Johnson**

Improving Signal Detection in Small Pharmacovigilance Datasets

*Johnson, H. Morris, J.*

Databases of medications taken in the first trimester of pregnancy, and any subsequent birth defects in the fetus are used to detect potential teratogens. Most analysis have focused on single drug-defect associations. However, teratogen exposure may result in several different defects, and several medications may have similar effects if they target the same biological pathways. We present a new approach that can incorporate information on groupings of defects and medications. We used simulated data to compare this new approach to other commonly used methods: Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), Du Mouchel's Gamma Poisson Shrinker (GPS), and Sequential Probability Ratio Test (SPRT).

The new approach examines all individual associations using the BCPNN, followed by categorisation into two groups (pairs with some evidence, pairs with no evidence). A biclustering algorithm is then used to form clusters of two or more drugs with some association to two or more of the same defects. The evidence required for a drug-defect pair to be part of a cluster is set slightly lower than traditional BCPNN criteria. Drug-defect pairs identified as meeting the traditional BCPNN criteria, or part of a cluster, are then considered as requiring further investigation.

Frequency tables of the number of pregnancies according to birth defect and medication exposure were simulated for 379 baseline-risk and 27 high-risk (5 times baseline risk) drug-defect pairs, for 3 sample sizes (approximate mean frequency of 2.5, 6 and 12 per pair). The power, type 1 error, and positive predictive value of each method was calculated, and simulations repeated until the Monte-Carlo standard error was <0.05 for each measure.

Within the smallest sample size, the new approach had greatest power to detect true associations, while maintaining the type 1 error of the BCPNN. The GPS and SPRT both had lower power and type 1 error than other methods. Differences in power between methods reduced with increasing sample size. This new approach may be of particular use in birth defect datasets which are typically smaller than the large spontaneous reporting datasets that other methods are tailored towards.

**55. Miss Hannah Johnson**

Modelling EUROCAT Congenital Anomaly Prevalence Trajectories Using Splines

*Johnson, H., Morris, J.*

Birth defects are structural or functional changes to the body that are present from birth, and are a major cause of morbidity and mortality, affecting approximately 2-3% of births. EUROCAT is a network of population-based registries that aim to provide epidemiological information on birth defects across Europe, including facilitation of early warning of new teratogenic exposures and clusters. Each year EUROCAT investigates prevalence trends over time for birth defect subgroups using Generalised Linear Models (GLMs) for individual registries, and Generalised Linear Mixed Models (GLMMs) for pan-European trends. However, these models assume any increasing or decreasing trends are constant across the time period. This assumption can be

relaxed by modelling with Generalised Additive Models (GAMs) and Generalised Additive Linear Mixed Models (GAMMs), also known as splines. These alternative models may provide a better representation of the true trends within these populations.

Prevalence trends for 26 individual registries for 94 birth defect subgroups were modelled using both GLMs and GAMs. Poisson models with log-links were used with the outcome number of cases, predictor centred year (2010-2019), and offset log-total number of pregnancies in the population. GAMs additionally used penalised thin-plate splines with a null space dimension of 0.5 and maximum number of knots set to 1 less than the number of years, with restricted maximum likelihood (REML) estimation. Pan-European trends were modelled using GLMMs and GAMMs with random intercepts and slopes by registry. GAMMs also used thin-plate splines with a null space dimension of 0.5 and REML estimation.

Trends within individual registries were modelled better by the GAMs than the GLMs. The more flexible GAMs were able to show where trajectories changed within the 2010-2019 period, such as where prevalence was increasing or decreasing for the first few years and then has levelled off, or vice versa. 178 GAM models (7.3%) showed a trend with moderate to strong evidence of increasing or decreasing trajectory ($p<0.05$), with an estimated degrees of freedom greater than 1.4 (suggestive of at least some curvature). For the pan-European trends, the GLMMs and GAMMs performed similarly, with splines reducing to a linear or almost linear trajectory.

# Session 2, 12:00–13:00

**56. Mr. Emil Joseph Vergara**

Systemic and mucosal immune responses after a single dose of two candidate intranasal subunit vaccines in mice with pre-existing lung mycobacterial immunity

*Vergara, E.J., Tran, A., Reljic, R.*

Tuberculosis (TB) is a major global health threat that claims 1.5 million lives annually. Treatment options for TB, drug sensitive or otherwise, are long especially in cases of multi-drug resistant TB (MDR-TB), wherein cure rates are also exceptionally low and costly. Post-exposure vaccination is an attractive therapeutic strategy for TB patients with the aim of working side-by-side with antibiotic therapy to either reduce the duration of treatment, improve cure rates, and lower the incidence of drug toxicities. Skewing pre-existing mucosal and systemic immunity towards a more protective phenotype is vital for the success of a post-exposure vaccine. In this study, two subunit vaccine candidates, Spore-FP1 and Nano-FP1, were delivered as a single intranasal dose to mice with pre-existing lung mycobacterial immunity elicited with Mycobacterium bovis BCG. Analysis of lung mucosal T cell responses showed an increasing trend in the frequency of tissue resident memory T cells, and antigen specific effector CD4 and CD8 T cells with a Th1 cytokine (IFN? and TNF?) signature among mice that received candidate vaccines. Significantly greater antigen specific effector CD4 and CD8 Th1 responses were also seen from splenocytes of immunised mice demonstrating potent boosting of systemic cellular immune responses. Measurement of antigen-specific IgG and IgA from blood and bronchoalveolar lavage fluid also revealed enhanced systemic and local humoral immune responses among immunised animals. Lastly, immunised mice exhibited lower bacterial burden in the lungs after high CFU challenge with M. bovis BCG. These results support further testing of Spore-FP1 and Nano-FP1 as post-exposure TB vaccines.

**57. Miss Hansween Kaur**

Calmodulin inhibition by the membrane permeant peptide inhibitor, mTrp, prevents Ca2+-dependent inhibition of gap junction coupling in human endothelial cells

*Hansween Kaur, Katalin Torok, Tom Carter*

Background: Endothelial cells are connected together by intercellular ion channels called gap junctions (GJs) that allow them to exchange nutrients, small molecules such as secondary messenger molecules, and respond synchronously to physiological activation. The permeation properties of GJs can be regulated by a wide range of intracellular signals including elevations of intracellular free calcium ion concentration ([Ca2+]i). Elevated [Ca2+]i closes GJs and is particularly important in helping to protect the endothelial monolayer when blood vessels are injured or damaged. The ubiquitous cytosolic calcium sensor Calmodulin (CaM), has been implicated in regulating gap junction coupling (GJC) in response to increases in [Ca2+]i. To study calmodulin-dependent processes in intact living cells membrane permeant peptide inhibitors based on the smooth muscle myosin light chain kinase CaM recognition site (mTrp peptide) have been developed (Thorogate and Török, Cell Science, 2004).

Aim: To quantify mTrp modulation of Ca-regulated GJC in confluent monolayers of human umbilical vein endothelial cells (HUVEC) in tissue culture.

Methods: GJC was monitored by intercellular spread of an extracellularly applied fluorescent molecule, lucifer yellow (LY), following formation of a defined mono-layer lesion. LY spread was objectively quantified using custom ImageJ analysis plugins described in Dydowiczova et al 2020, Sci Rept, 10, 730.

Results: Characterization of the scratch assay confirmed that modulation of GJC could be detected and quantified. To examine Ca2+-dependent GJC, HUVEC were pre-treated (8 minutes) with vehicle (0.01%DMSO) or ionomycin (2µM) in the presence or absence of external Ca2+, prior to monolayer lesion. In the presence of external Ca2+ GJC was significantly reduced compared to vehicle control ($P<0.0001$, ANOVA). The reduction in GJC observed with ionomycin in the presence of external Ca2+ was reversed in a dose-dependent fashion by co-incubation with mTrp peptide (7µM, 17µM) but not the control peptide (mCTRL).

Conclusions: GJC in HUVEC are regulated by elevated [Ca2+]i. The membrane permeant CaM inhibitory peptide mTrp prevented Ca2+-mediated closure of GJs in HUVEC at low micromolar concentrations. Because the myr-trp peptide is a stochiometric blocker of CaM this suggests that HUVEC express low micro-molar concentrations of CaM.

**58. Miss Jemma Keefe**

Mature Oligodendrocyte Population Dynamics in Physiological and Pathological Aging

*Keefe J, Hainsworth A*

Background. Mature oligodendrocytes (OLs) are responsible for axon myelination in the brain. Age-related cognitive deterioration, as well as impaired resistance to neurological pathology, occurs secondary to structural brain changes. This includes decreased myelin volumes suggestive of OL involvement. Structural changes occur to a greater extent in cerebral small vessel disease (cSVD); therefore, we hypothesise OL densities will decrease with increasing age as well as in cSVD.

Methods. This was a blinded study whereby immunohistochemistry was performed on post-mortem human brain specimens (N=28, Mean age=83.9+-8.74, 9F/6M) using an antibody targeting Nogo-A+ to identify OLs. Microscopic images of specimens, produced with digital pathology software, were analysed using manual counting and image analysis software, FIJI (ImageJ), to generate a labelling index (OL/total cells, %), OL density (OLs/mm2) and area fraction (AF%). Statistical analysis conducted using SPSS.

Results. Nogo-A+ OLs included small, round cells with a thin layer of brown-stained cytoplasm surrounding a nucleus. There was a significant positive correlation between age and OL densities ($rs=0.619$, $p=0.011$) as well as labelling index ($rs = 0.624$, $p=0.010$) in white matter (WM) tissue. No inter-sex variation in OL populations was found. Our preliminary results also indicate a trend of decreased OL densities in cSVD, with indications of similar trends in Alzheimer's disease (AD) and Lewy Body Dementia (LBD). This study shows trends of decreasing OL densities at increasing distances from the sub-ventricular zone (SVZ).

Conclusion. There was evidence against the hypothesis that OL densities decrease with age, however this is heavily disputed by previous literature. The causative mechanisms affecting OL populations in age occur to a greater extent in neurological pathology, i.e., cSVD, AD and LBD, and thus OL densities are lower than in healthy specimens. This may underlie myelin decreases in these neurological pathologies responsible for cognitive and functional alterations beyond the scope of physiological aging.

**59. Ms Julia Kutschenreuter**

Neutrophil-dependent secretion of the biomarker LRG1 in Tuberculosis and its role in fibrosis development

*Julia Kutschenreuter, Maria Cristina Loader, Daniela E. Kirwan, Robert H. Gilman, Jon S. Friedland and Deborah L.W. Chong*

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is responsible for more than 1 million deaths annually. In addition, up to 94% of recovered TB patients have decreased lung function and fibrosis. Serum Leucine-rich alpha-2 glycoprotein-1 (LRG1) concentrations are elevated in TB patients and decreased after therapy, but its role in TB pathogenesis and the source of LRG1 in TB patients is unknown.

I hypothesise that neutrophils are key regulators of LRG1 secretion, and contributes to fibrosis development in TB patients.

Neutrophils were isolated from peripheral blood from healthy donors and secretion of LRG1 after Mtb infection or stimulation with conditioned media from Mtb-infected monocytes (CoMTb) was quantified by ELISA. LRG1 secretion from CoMTb-stimulated bronchial epithelial cell supernatants were also measured. Histology of LRG1 expression was performed on lymph nodes sections from TB patients and control lungs.

To study the pro-fibrotic effects of LRG1, primary human lung fibroblasts were stimulated with purified LRG1 and collagen production was quantifed using fluorescence microscopy. The therapeutic potential of neutralising LRG1 in vitro was assessed with a novel LRG1 blocking antibody (15C4).

LRG1 secretion by neutrophils is significantly higher after Mtb infection or CoMTb stimulation compared to controls (0.56 vs 1.84 ng/ml, $p=0.0159$ and 0.54 vs 2.23 ng/ml, $p<0.01$ resp.)

Bronchial epithelial cells stimulated with CoMTb also show increased LRG1 secretion compared to controls (0.75 vs 1.90 ng/ml, $p<0.01$).

Primary human lung fibroblasts treated with LRG1 leads to significantly increased collagen-1 production and ??-SMA expression (fibroblast differentiation marker) in a dose-dependent manner compared to control. Neutralising LRG1 with 15C4 blocks these fibrotic changes.

These results show that neutrophils are a key cellular source of LRG1 in a monocyte-dependent network in TB and upon direct infection with Mtb. Analysis also shows bronchial epithelial cells are an additional source of LRG1.

LRG1 drives lung fibrosis and can be blocked using a novel antibody in vitro, and represents a potential adjuvant therapy to prevent fibrosis following TB infection.

**60. Miss Katie Latham**

Characterisation of the Interaction of the Zinc Finger Antiviral Protein (ZAP) with Human Cytomegalovirus.

*Katie Latham, Blair Strang*

Zinc finger Antiviral Protein (ZAP) is encoded by the human gene ZC3HAV1. It can be classified as a pattern recognition receptor as it directly binds viral ssRNA to cause viral inhibition through nucleotide degradation. It elicits its antiviral activity against a diverse range of RNA viruses but its effect on DNA viruses is not well

understood. Here, we investigate how ZAP interacts with the DNA virus Human Cytomegalovirus (HCMV), a widespread pathogen that causes life-threatening clinical symptoms in immunocompromised individuals.

We analysed which ZAP isoforms are present in HCMV-infected cells using western blotting. Viral titre assays and quantitative PCR with ZAP knock-out cells were used to determine ZAP's effect on viral infectivity and replication. The amount of interferon produced during infection was measured using GFP confocal microscopy. Bioinformatics, including use of the NCBI database and STRING software, was used to investigate the alternative splicing of the ZC3HAV1 gene, and the interactions of HCMV and human proteins linked to interferon production.

We determined all four isoforms were present in HCMV-infected cells, with the most abundant isoforms having different induction pathways; ZAP-L was constitutively expressed, and ZAP-S was interferon-induced. ZAP causes viral inhibition of HCMV through reduction of in the number of viral genomes present. We also identified two HCMV proteins, UL2 and UL5, that may have antagonistic effects on interferon production through their interaction with the human proteins CREBBP and ANKRD13A.

Our findings demonstrate that ZAP acts as both a restriction factor and an interferon-stimulated gene in response to HCMV infection and exerts its antiviral activity against HCMV by inhibiting viral replication.

**61. Dr Fiona Leggat**

"How are some people coping and I'm not?": Experiences and strategies when navigating the everyday challenges of living with Long Covid.

*Leggat, F., Heaton-Shrestha, C., Fish, J., Siriwardena, A.N., Domney, A., Rowe, C., Patel, I., Parsons, J., Blair, J., Jones, F.*

Background: Long Covid is a complex condition characterised by multiple, interacting, and fluctuating symptoms which persist after the contraction of the SARS Covid-19 virus. Officially recognised by the World Health Organisation in 2021, 2.1 million people in the UK are estimated to be experiencing the condition.

NHS commissioning guidance recommends the provision of self-management support. Yet, such provision and access to services across the UK is varied. Qualitative studies have begun to highlight strategies to self-manage day-to-day life. Strategies reported include pacing, rest, and dietary modifications. However, while strategies have been successful for some, they have been unhelpful for others. This research sought to explore and illustrate how people with long Covid manage their everyday lives, and what may influence the use of different strategies.

Methods: The study comprised part of a wider accelerated experienced based co-design (AEBCD) process within the Long Covid Personalised Self-management support and Evaluation (LISTEN) project. Together with people living with long Covid, the co-design process sought to develop the LISTEN intervention. This study reports on the narrative interviews which were undertaken in the co-design process.

Eighteen adults living with long Covid participated in the study. Remote semi-structured interviews were used to explore participants stories of long Covid including their initial Covid-19 experiences, their long Covid symptoms and day-to-day challenges, and their strategies to navigate everyday life with the condition. Data were analysed using a reflexive thematic analysis.

Findings: Three themes were constructed from participants experiences; landscapes behind long Covid experiences, the Long Covid spectrum of experience, and strategies to navigate everyday life. Highlighting the messiness and diversity of long Covid experiences, these themes portray a complexity and interconnectedness. Management strategies reported included seeking medical reassurance, developing self-awareness, self-discovery of 'safe' ideas and prioritising what works for you.

Conclusions: Long Covid is unpredictable, fluid, and non-linear over time. People's experiences of the condition are unique and should be treated as such through personalised care with attention to the person's story and

the evolving contextual Long Covid narrative. The development of self-awareness and self-discovery can lead to symptom stability, considered as progress for those with Long Covid.

**62. Mr Chunhei li**

Diagnosis of Splenic Artery Aneurysm

*CHUNHEI LI, James Budge, Iain Roy*

Background: Splenic Artery Aneurysms (SAA) is the most common type of Visceral Artery Aneurysm (VAA). SAA is often asymptomatic and hence incidental findings on CT scans. The national treatment of SAA's is varied but rapidly increasing size often warrants intervention. Accurate radiological classification is hence essential to help guide clinical decision-making. To update there is no standardised way to measure the size or categorised the radiological characteristics of SAAs. Given the subtle appearance of SAAs they may be often left unidentified during the reporting. Therefore its prevalence could be well underestimated.

Aims: In this study, we aimed to develop a radiological protocol to standardise the size and characteristics reporting of SAAs.

Objectives:

- Evaluate a method to measure the size of SAA
- Evaluate a method to quantify the calcification of SAA
- Analyse the inter and intra-observer variability of these measurements
- Assess the inter and intra-observer variability of differentiation of saccular or fusiform SAAs

Methodology: This study represents a retrospective cohort study at a single tertiary center. Patients were identified using the local radiological scan database (Soliton) which was queried for scans in the last 10 years

A total of 170 patients were found: 115 SAAs were confirmed with reported size on the index scan; 45 SAA were confirmed with no reported size, 10 SAA were not confirmed but suspected to have SAA.

The Department of vascular surgery has collaborated with the Department of Radiology at St George Hospital, and we have pioneered a 9-step approach to identify SAA. We have also suggested two conventional methods to measure the calcification and size of the SAA

To measure the size of diameters of the SAA

- Conventional method: record maximal diameter in all three planes coronal, sagittal, transverse
- Semi-automatic centerline with 2 paired maximum diameters

Measurement of calcification

- Circumferential calcification score - an estimate of maximal circumferential calcification, this will later be converted into the grades

We will aim to analyze the diagnostic sensitivity, inter and intra-variability of the SAA

**63. Miss Li Ling Lee**

Copy Number Variant Analysis in the Primary Lymphoedema Cohort

*Lee, LL., Dobbins, S., Pittman, A.M., Ostergaard, P.*

The lymphatic system plays a crucial role in regulating fluid homeostasis and facilitates immunological function. Primary lymphoedema (PL) is a lifelong, disabling condition caused by underlying genetic defects leading to lymphatic dysfunction. This rare disease (1 in 6000) causes lymph fluid retention which results in distress, swelling of the affected limbs, recurrent cellulitis, discomfort, and significant skin changes. Understanding the genetic basis of this condition will aid both diagnosis and hopefully identify new avenues for treatment. Historically, genetic studies for the assessment of rare disease have been limited to single-nucleotide polymorphisms (SNPs), rare sequence variants, and short indels analysis in whole exome sequencing (WES).

Numerous studies, however, have also uncovered pathogenic Copy Number Variations (CNVs) across a large range of diseases, with pathogenic CNVs identified in approximately 10% to 20% of individuals with idiopathic intellectual disabilities. CNVs include deletions, insertions, and duplication events in the human genome. These structural genomic alterations can range from sub-microscopic events to complete chromosomal aneuploidies. CNVs cause a spectrum of phenotypic effects with most CNVs associated with a disease phenotype altering the genomic copy number of dosage sensitive gene(s).

To date, we are only able to provide a genetic diagnosis for 40% of PL cases. We anticipate that uncovering the CNVs associated with PL will allow us to identify additional genetic causes and further understand molecular pathways, and mechanisms involved in disease pathogenesis. Therefore, this study aims to develop a standard bioinformatic pipeline for CNV calling analysis in WES data and elucidate the spectrum of CNVs in our PL cohort. The establishment of additional genetic diagnosis will lead to appropriate referrals for therapy, accurate molecular diagnosis and formation of novel or more effective treatment.

**64. Dr Clare Logan**

CandiRES: Relationship of Antifungal Exposure to Emergence of Candida Resistance

*Allebone-Salt P, Logan C, Mazzella A, Lonsdale D, Hemsley C, Wyncoll D, Saha R, Schelenz S, Abdolrasouli A, White L, Price J, Harrison T, Bicanic T.*

Intensive Care patients are at a high risk of invasive candidiasis and subsequently antifungal use is high in this setting. However, our understanding of the impact of antifungal exposure on colonising Candida flora and the emergence of fungal resistance is limited. CandiRES is a prospective multi-site observational study, recruiting ICU patients on antibiotics and with at least one risk factor for invasive candidiasis. During the ICU admission, twice-weekly serial swabs for Candida culture are taken and antifungal prescribing data is collected. The incidence rate of colonisation and invasive infection, Candida species profile, change in antifungal susceptibility and the emergence of heteroresistant sub-populations is assessed. Those exposed and unexposed to antifungal therapy are compared to evaluate the impact of drug exposure on the evolution of antifungal resistance. Patients with invasive candidiasis undergo serial BDG, PCR and time-to-culture blood culture positivity testing, with the aim of identifying an accurate treatment response biomarker. Here we present an interim analysis of our results. To date, 183 participants have completed the study, almost 50% of which had at least one course of antifungals, most commonly anidulafungin. We will present the epidemiology of colonising Candida species across over 800 isolates, the most common of which are C albicans, C glabrata and C dubliniensis, evidence suggesting the emergence of heteroresistant Candida populations through population analysis profiling, and our MIC results. We will also present the BDG results for 13 patients with invasive candidiasis and its association with certain Candida species.

**65. Mr Luka Lozo**

Development of a novel bright and superfast genetically encoded glutamate sensor S104T iGluSnFR3

*Lozo L., Tran O., Hughes, H., Török, K.*

Imaging glutamate neurotransmission using genetically encoded intensity-based glutamate sensors has opened a new horizon in imaging brain activity. The recently developed iGluSnFR3.v857 (1) has improved brightness, but slow off-kinetics, limiting its application to resolving low frequency action potential firing. Our aim was to generate variants with faster off-kinetics while preserving the high brightness and dynamic range of iGluSnFR3.v857. Our strategy was to make mutations to amino acid residues at the glutamate binding site of the sensor to affect the affinity and kinetics of the sensor. A selection of mutations that we have previously used to generate faster variants of the previous iGluSnFR generation (2) were introduced in iGluSnFR3.v857 and the biophysical properties of the novel iGluSnFR3.v857 variants were determined.

Single amino acid variants were generated by site-directed mutagenesis, the variant proteins were expressed in BL21 cells and purified by affinity chromatography. Glutamate binding affinity was measured by continuous titration with glutamate at excitation and emission wavelengths of 492 nm and 515 nm, respectively, at 20°C (Fluorolog3, Horiba Scientific). Kinetic measurements of glutamate association and dissociation were carried out by stopped-flow fluorimetry (TGK Scientific). The assay buffer for all measurement was phosphate buffered saline, pH 7.4.

Four variants were generated: D57A, D57R, R56K and S104T. Glutamate binding induced fluorescence enhancement values were: iGluSnFR3.v857, 26-fold; D57A, 16-fold; D57R, 23-fold; R56K, 6-fold and S104T, 42-fold. Off-rates were: iGluSnFR3.v857, 71 ± 3 s-1; D57R, 23 ± 1 s-1; S104T, 340 ± 48 s-1. Maximum on-rates of iGluSnFR3.v857 and the S104T variant were 1399 ± 43 s-1 and 832 ± 148 s-1, respectively. Finally, dissociation constant values for iGluSnFR3.v857 and the S104T variant were 0.373 ± 0.003 mM and 3.18 ± 0.05 mM, respectively.

In summary, the S104T mutation of iGluSnFR3.v857 successfully increased the fluorescence dynamic range by 60 %, increased the off-rate ~5-fold and reduced the affinity 5-fold. Thus, the S104T variant represents a significant improvement on iGluSnFR3v.857 and has great promise for imaging glutamate neurotransmission in health and disease.

1 Aggarwal et al., bioRxiv.2022.02.13.480251

2 Helassa et al., PNAS (2018) 115 (21) 5594-5599

**66. Mrs Merry Macdonald**

Percutaneous Electrical Nerve Stimulation (PENS) following division of the left maxillary branch of the trigeminal nerve

*Macdonald, M. Alkhataybeh, R. Tavakkoli, M.*

Background and Aims: A 58 year old lady presented with severe left sided facial pain and anaesthesia at the V2 distribution following surgery and radiotherapy. The initial pathology was adenoid cystic carcinoma (ACC) left pterygopalatine fossa and a surgical procedure warranted resection of tumour causing division of the left maxillary branch of the trigeminal nerve. Subsequent pain was refractory to multiple medication including opioids and antineuropathics. A course of treatment with Percutaneous Electrical Nerve Stimulation (Algotec©) was then initiated.

Methods: PENS was performed below the nerve injury for 25 minutes using an Algotec© 80/100 single bevel probe using a standard PENS protocol and repeated again after eight months

Results: Pain and sensitivity were significantly reduced (65%) and the size of the area of allodynia was reduced by 40% following the 1st treatment. The patient was able to reduce her use of Fentanyl patch down to 12mcg/h from 37mcg/h. She showed significant clinical improvement, illustrated by reduction in Brief Pain Inventory scores which was sustained for six months. As such the treatment was repeated with continued reduction in pain and allodynia.

Conclusion: Percutaneous nerve stimulation below the nerve injury site can be beneficial in reducing neuropathic pain when access to neural pathways above the injury level is anatomically limited.

**67. Dr Hamish MacLachlan**

Outcome of a nationwide screening programme in young individuals

*H. Maclachlan1, R. Bhatia1, H. Dhutia2, S. Fyyaz1, N. Chatrath1, S Marwaha1, J. Basu3, C. Miles1, G. Finocchiaro1, S. Gati4, M. Specterman1, M. Tome1, A. Malhotra1, E. Behr1, S. Sharma1, M. Papadakis1 - (1) St Georges Hospital Ltd, London, United Kingdom*

Background: Sudden cardiac death (SCD) seemingly affects young, healthy individuals and is therefore recognised as an important public health concern for athletes and non-athletes. However, systematic population screening is not recommended in the United Kingdom (UK). Concerns include the low reported incidence of SCD in young individuals, the efficacy of the electrocardiogram (ECG) and the lack of robust evidence on cardiac screening. We sought to determine the diagnostic yield of a nationwide cardiac screening programme in young individuals. Importantly, we sought to report on the frequency of false-negative screen-test results, which is underrecognized in the literature, and the incidence of sudden cardiac arrest (SCA) and SCD amongst individuals who underwent screening.

Methods: From 2007 through 2018, 104,369 consecutive individuals, aged 14 to 35 years, underwent voluntary cardiac screening (62% were male, 91% were non-athletes). Initial evaluation consisted of a health questionnaire (HQ), ECG, and clinical consultation. Selective on-site echocardiography was available at the discretion of the consulting physician. Clinical outcomes were sourced from the Office for National Statistics-Hospital-Episode-Statistics database and an online HQ.

Results: During screening 280 (0.27%) individuals were found to have a cardiac condition associated with SCA/SCD and 115 received potentially life-saving treatments. A further 166 (0.16%) with congenital or valvular abnormalities were identified. During a mean follow-up of 6.2 ± 2.5 years, an additional 86 individuals, considered to have normal screening, were found to have a cardiac condition associated with SCA/SCD.After screening there were 86 deaths. Cardiac disorders accounted for 20 deaths (23%), all of which were sudden. In addition, 15 individuals survived a SCA. Primary electrical disorders accounted for 21 (60%) of the 35 cases of SCA/SCD, followed by cardiomyopathies (n=6), and congenital or acquired coronary artery disease (n=5). On the basis of a total of 626,550 person-years (PY), the combined incidence of SCA/SCD was 1:17,901 PY (5.6 per 100,000 PY). Males were at 3.5-fold higher risk than females (1:12,488 PY vs 1:44,067 PY, $p < 0.01$). For prevention of SCA/SCD the programme's sensitivity was 19.4% with a specificity of 97.5%. For identifying conditions associated with SCD, the programme's sensitivity was 76.5% with a specificity was 97.8%.

Conclusion: Diseases that are associated with SCD were identified in 0.27% of young individuals who underwent cardiac screening. A further 86 (0.08%) conditions were identified after screening. The incidence of SCA and SCD was 5.6 per 100,000 person-years, which is considerable higher than previous estimates in the general population. Most of these events were due to confirmed or presumed primary electrical disorders that had not been detected on screening.

**68. Dr Hamish MacLachlan**

Outcomes of a nationwide cardiac screening programme in young individuals

*Dr. Hamish Maclachlan, Dr. Raghav Bhatia, Dr. Harshil Dhutia, Dr. Saad Fyazz, Dr. Nikhil Chatrath, Dr. Sarandeep Marwaha.*

Background: There is limited information on the impact of screening for conditions associated with sudden cardiac arrest (SCA) and sudden cardiac death (SCD) in young individuals, outside the context of elite sport. We sought to determine the diagnostic yield of cardiac screening in young individuals and the incidence of SCA and

SCD amongst individuals who underwent cardiac screening. Importantly, for the first time on a nationwide level, we examined the frequency and implications of false-negative screen-test results.

Methods: From 2007 through 2018, 104,369 consecutive individuals, aged 14 to 35 years, underwent voluntary cardiac screening (62% were male, 91% were non-athletes). Initial evaluation consisted of a health questionnaire (HQ), ECG, and clinical consultation. Selective on-site echocardiography was available at the discretion of the consulting physician. Clinical outcomes were sourced from the Office for National Statistics-Hospital-Episode-Statistics database and an online HQ.

Results: During screening 280 (0.27%) individuals were found to have a cardiac condition associated with SCA/SCD and 115 received potentially life-saving treatments. A further 166 (0.16%) with congenital or valvular abnormalities were identified. During a mean follow-up of 6.2 ± 2.5 years, an additional 86 individuals, considered to have normal screening, were found to have a cardiac condition associated with SCA/SCD. After screening there were 86 deaths. Cardiac disorders accounted for 20 deaths (23%), all of which were sudden. In addition, 15 individuals survived a SCA. Primary electrical disorders accounted for 21 (60%) of the 35 cases of SCA/SCD, followed by cardiomyopathies (n=6), and congenital or acquired coronary artery disease (n=5). On the basis of a total of 626,550 person-years (PY), the combined incidence of SCA/SCD was 1:17,901 PY (5.6 per 100,000 PY). Males were at 3.5-fold higher risk than females (1:12,488 PY vs 1:44,067 PY, $p < 0.01$). For prevention of SCA/SCD the programme's sensitivity was 19.4% with a specificity of 97.5%.

Conclusion: Diseases that are associated with SCD were identified in 0.27% of young individuals who underwent cardiac screening. A further 86 (0.08%) conditions were identified after screening. The incidence of SCA and SCD was 5.6 per 100,000 person-years, which is considerable higher than previous estimates in the general population.

**69. Miss Nika Majidi**

An Evaluation of the Epilepsy Surgery Service at St George's Hospital

*Majidi, N*

The aims of this audit were to assess the timeframe for investigations and referrals for epilepsy surgery to be completed across all patients in the database at St George's Hospital (SGH), to assess the number of cases surgery was not advised and to evaluate the outcomes following surgical treatment.

This is a retrospective study using a contemporary database and electronic health records. The patients included were those over 18-years-old who were assessed in the SGH epilepsy surgery pathway prior to June 2021. The data collected included: age of onset of epilepsy, dates of referral for pre-surgical work-up, when investigations and multidisciplinary team (MDT) meetings were completed, and the outcomes of surgery. Data was collected and analysed using excel tools.

95 patients were included (male to female ratio: 1:1.6) with a mean age of 36 years (range: 18-71 years). 17 out of 95 patients underwent surgery; 58 patients received ongoing medical management; 20 patients had vagal nerve stimulator insertion and 12 patients were lost to follow-up. Contraindications for surgery included a lack of seizure focus found, bilateral onset of seizures or risks of surgery outweighing benefits. 59% had diagnosed epilepsy for up to 20 years before referral for work-up and only 26% were referred within 10 years. 93% had investigations completed within 2 years following referral whilst 59% had completed investigations within one year. Factors delaying work-up included temporary seizure remission and being lost to follow-up. 11 of the 17 patients who underwent surgery were seizure free at their last follow-up (Engel class I) with five patients stopping all anti-epileptic medication. One patient exhibited no benefits from surgical treatment (Engel class IV). 14 of the 17 patients received post-operative neuropsychometry and neuropsychiatry assessments.

In conclusion, surgical management improved seizure control with 64.7% entering complete remission. The database had missing data from various fields. This has been addressed with the creation of a pre-surgical MDT

proforma, embedded in the patient record. A future audit of this proforma is required. Delay in referrals can have detrimental effects on patient's socio-economic outcomes and sudden unexpected death in epilepsy. Actions to improve the pathway include earlier referrals for work-up, reducing cases lost to follow-up and ensuring all patients undergo post-operative neuropsychology and neuropsychiatry input.

**70. Dr Elena Marcus**

The time-distributional effects of night-time aviation noise exposure on annoyance and sleep disturbance

*Marcus, E., Toomse-Smith, M., Basner, M., Trow, J., Marcheselli, F., Mandalia, D., Steinbach, R., Morris, J., Gibbs, G., Clark, C.*

This paper will report on the methodology for a new UK study of aviation night-noise exposure on health. Funded by the United Kingdom Department for Transport (DfT), the study is examining the effects of aviation night-noise exposure for a range of time-periods on sleep disturbance and annoyance. The study involves (1) a cross-sectional survey of 4,000 participants living near eight UK airports to assess associations of aircraft noise exposure at night and subjective sleep disturbance and annoyance, and (2) an objective sleep disturbance study of 170 participants, where physiological assessments of sleep disturbance will be linked to aircraft noise exposure and events at the participant's home. The study will deliver exposure-response functions showing how time-averaged metrics such as LAeq,8h, LAeq,1h, N60 and event-related metrics (LAmax, Sound Exposure Level) relate to subjective and objective sleep disturbance, and annoyance, which could be used to inform updates to the DfT's Transport Analysis Guidance (TAG) and subsequently aviation night-noise policy in the UK. It will also be possible to examine effect modification, quantifying whether some population groups may be more vulnerable to the effects of aviation night-noise on health.

**71. Miss Assal Massroor**

Do we manage elective paediatric orthopaedic conditions at St George's Hospital according to the 'Getting It Right First Time' (GIRFT) standard?

*Assal Massroor (Year 3 Medical Student at St George's University of London) and Yael Gelfer (Consultant Paediatric Orthopaedic Surgeon).*

Background: GIRFT is an NHS programme developed to address unwarranted variation in the provision of services across England. Recommendations outlined by GIRFT serve as a tool to quantify standard of care, improve and drive clinical excellence as well as resource acquisition.

Aims: Primary aim is to benchmark current management standards of elective paediatric orthopaedic conditions at St George's Hospital (STGH) against the paediatric orthopaedic GIRFT recommendations. Secondary objective is to devise an action plan with a timeline of implementation of items that are yet to meet the standard.

Standards audited: Seven recommendations subdivided into 25 actions published in the national paediatric orthopaedic GIRFT report for improving the care of children who are vulnerable. This audit is examining common elective orthopaedic conditions such as developmental dysplasia of the hip, clubfoot, cerebral palsy, osteoarticular infections, and 'managing variants of normal'.

Methods: Recommendations from the national GIRFT paediatric orthopaedic report were reviewed, and seven recommendations subdivided into 25 actions, relating to the management of elective conditions, were selected. These were subsequently stratified into 'national', 'regional', or 'local' action required. For regional and local recommended actions, the status of completion and plan for action was reported based on a consensus among paediatric orthopaedic consultants involved with both regional and local care of these conditions, alongside the STGH GIRFT observation report. Descriptive statistics were used for analysis.

Results: Out of the seven recommendations and 25 actions outlined by the national paediatric orthopaedic GIRFT report, 16 were found to require action on a local level (64%), 11 on a regional level (44%), and 9 on a national level (36%). The current standard at St George's University Hospitals showed 11 regional and local recommendations were already in place (57.9%), five to be in progress (26.3%), and three to be in need of action (15.8%)

Conclusion:The majority of the audited elective paediatric orthopaedic conditions at STGH were found to meet the national GIRFT standard (57.9%). Where current services do not meet GIRFT standards, i.e. are either 'in progress' or 'yet to be reviewed', the plan is to implement GIRFT recommendations and re-audit the implementation in a year.

**72. Dr Natasha Matthews**

Training tomorrow's doctors: the Medical Student Leadership Scheme

*Matthews NR, Wright H, Malhotra AM, Kanga K, Kenny C, Chingono J*

Context: Between April-May 2021, 14 medical students undertook a 'virtual' elective run by the Faculty of Leadership and Management (FMLM).

Issue: Medical leadership appears neglected within the undergraduate curriculum. Upon joining the scheme, 73% of students said their leadership teaching had been 'poor' or 'very poor'. This negative experience requires addressing.

Intervention: A team of Clinical Fellows planned and produced a programme of leadership teaching to complement the core content delivered by FMLM. The fellows facilitated problem-based learning sessions, interactive webinars and lunchtime lectures from medical leaders covering over 10 national organisations.

Strategy for Improvement: Over the six-week elective, 19 sessions were delivered. Students were invited to give informal feedback after every session by responding to the questions "what went well?" and "even better if". This informed real-time change to the programme, for example, adjusting session length and interactivity.

Measurement of improvement: Survey results were collected through SurveyMonkey. The use of Likert scales facilitated analysis with clear improvements across all domains. Students were more interested in undertaking leadership and management roles in the future, had increased confidence to challenge poor practice and a better understanding of the healthcare system and organisations.

Impact: Results from the post-elective survey clearly demonstrated improvements in the groups' understanding of medical leadership, the wider healthcare landscape and enthusiasm to engage in leadership activities in their future career. We anticipate this will help this cohort of students to identify and successfully obtain leadership roles.

Lessons Learnt: This project provided rich learning for Clinical Fellows developing skills required to deliver leadership training remotely to a varied cohort of students. It provided an opportunity for fellows to reflect on their leadership and mentoring styles. The next challenge will be to ensure that lessons learnt are shared with incoming Clinical Fellows to improve and develop the next elective programme.

Messages for others: The provision of leadership training at medical school is variable; however, a combination of a virtual elective fellowship experience and a leadership educational programme demonstrated improvements in students' understanding and desire to engage with medical leadership.

**73. Dr Sile Molloy**

Sub-EFFECT: Pathophysiology and clinical outcomes of subclinical cryptococcal meningitis

*Síle F Molloy*2, Rachel Wake* (*equal contributions)*

Subclinical cyptococcal meningitis (CM) occurs in around a third of patients with advanced HIV disease and cryptococococcal antigenaemia; defined as positive cerebrospinal fluid (CSF) cryptococcal antigen (CrAg), microscopy (India Ink) or culture for Cryptococcus spp in the absence of symptoms or signs of meningoencephalitis (severe headache or confusion). Little is known about the clinical implications of subclinical CM, since lumbar punctures (LPs) are not routinely performed in asymptomatic CrAg-positive patients. If diagnosed, subclinical CM is currently managed as per symptomatic CM, requiring admission to hospital for intravenous therapy and repeated lumbar punctures. However, subclinical CM is likely to represent an earlier stage in the clinical spectrum of cryptococcal antigenaemia, diagnosed prior to symptom onset and with a lower risk of mortality. Greater understanding of the pathophysiology of subclinical CM, and its clinical implications, will guide differential management of this group.

SubEFFECT is a prospective cohort study of patients with subclinical CM, diagnosed by LP, who are excluded from the EFFECT trial (phase III, randomised controlled trial of a novel combination antifungal regimen for patients with HIV, CD4 counts <100 cells/uL and asymptomatic cryptococcal antigenaemia). Patients will be recruited if they provide informed consent following diagnosis of subclinical CM, at five EFFECT trial sites in South Africa and Tanzania. Following initial clinical assessment, patients will be followed up by telephone calls for 6 months. A comparison group of patients with symptomatic CM will be recruited at the same sites (to subEFFECT in Tanzania, and to surveillance platform 'GERMS-SA' in South Africa) and followed up at the same time points. This study will aim to enrol 140 participants with subclinical CM over 2.5 years.

The primary outcome is 6 month all-cause mortality in patients with subclinical CM. Mortality will be compared to patients with asymptomatic cryptococcal antigenaemia and symptomatic CM attending the same study sites, as a secondary objective and assessed by level of cryptococcal burden in blood and CSF. Additionally, parameters of meningeal inflammation will be described in subclinical and symptomatic CM.

SubEFFECT findings will inform future management strategies, including consideration of an oral antifungal regimen for subclinical CM.

**74. Dr Sile Molloy**

EFFECT: Fluconazole plus flucytosine vs. fluconazole alone for cryptococcal antigen positive patients identified through screening: A phase III randomised controlled trial

*Sile Molloy*

Cryptococcal meningitis (CM) is estimated to cause 110,000 deaths globally per year, accounting for 15%-20% of all AIDS-related deaths.

Screening patients with low CD4 counts using a simple point-of-care test to detect cryptococcal antigen (CrAg) and treatment of CrAg-positive patients in advance of severe disease represents a practical and cost-effective approach to reducing mortality, with such screening programs now recommended in many SSA countries. Current pre-emptive treatment with fluconazole alone may be suboptimal with a significant number of patients going on to develop meningitis and die. More effective antifungal regimens are thus urgently required. In the phase III ACTA trial, a combined treatment of fluconazole and flucytosine was shown to be safe and effective in those with symptomatic meningitis, with mortality halved compared to historic cohorts treated with fluconazole alone.

The EFFECT trial is a phase III, multi-centre, pragmatic open-label, randomised controlled trial embedded in existing screening programs in South Africa, Tanzania and Vietnam. HIV-infected adults identified through routine laboratory screening as serum CrAg-positive in blood and who are also cerebrospinal fluid CrAg-

negative or who decline a lumbar puncture are being recruited following informed consent. Participants are randomised, 1:1, to receive either fluconazole alone (1200 mg/day, control arm/current recommended treatment) OR a combined regimen of fluconazole (1200 mg/day) plus flucytosine (25 mg/kg qds, intervention arm) for 2 weeks. Participants are seen in clinic on day 1 and 15 and contacted on days 3 and 9 by telephone for adherence counselling and at 1, 2.5 (10 weeks), 4 and 6 months to determine survival status. The primary end point of all-cause mortality at 6-months will be compared between the two groups. A total of 600 participants will be recruited over a 2.5-year period, beginning in October 2022. The trial will also assess progression to cryptococcal meningitis, tolerability and safety, and cost effectiveness.

A safe and potent oral treatment regimen, which could be administered to outpatients, could have a major impact on survival, and driving down AIDS-related mortality.

**75. Dr Phil Moss**

"I don't have time": strategies for increasing research engagement in emergency department clinical staff

*Jarman, H., Halter, M., Moss, P*

Aims, objectives and background: Clinicians who engage in generating research knowledge are more likely to implement findings in practice leading to better patient outcomes. Having an emergency department (ED) culture that gives significance to research is an important factor in supporting clinicians to develop the skill and ability to participate and perform research.

In 2018 the ED at St George's Hospital, London introduced an embedded research group with a dedicated leadership position, bringing together research delivery staff and clinical academics to increase the research culture in the department. This study aimed to investigate the impact of this model on research engagement amongst the ED clinical multi-disciplinary team.

Method and Design

A case study design approach was used involving:

- A registry of the research-related initiatives undertaken in the department

- Analysing the metrics of engagement in research activities by clinical staff, including number of publications and academic training uptake

Data were collected between April 2018 and March 2022.

Results and conclusion: Registry data show 41 distinct initiatives established in the time period led or delivered by the research group. These included face-to-face teaching, publication writing support, a research internship program and small grant funding. Research outputs (publications or conference abstracts) showed a 23-fold increase from two in 2018 to 47 in 2021.

The project to develop a research culture in ED has had a positive effect on both type and number of research-related activities across all clinical staff groups. This case study illustrates how research activities delivered close to clinical practice under visible, focused clinical research leadership can increase research engagement. Challenges of a clinically complex context were overcome by embedding a multidisciplinary clinical research unit, linking research delivery with clinical academic development. This model could be replicated in other settings.

**76. Dr Abteen Mostofi**

Factors associated with targeting error in deep brain stimulation

*Abteen Mostofi, Bryony Ishihara, Fotios Bourlogiannis, Michael G. Hart, Erlick A. C. Pereira*

Introduction: The efficacy of deep brain stimulation (DBS) surgery depends upon the accuracy of stereotactic electrode implantation at desired target loci. Post-implantation imaging allows comparison of electrode position to pre-operative plans and definition of targeting errors. This study uses real-world clinical data from a large single-centre case series to quantify DBS targeting errors and identify associated variables.

Methods: We performed a retrospective analysis of 86 patients (171 electrodes) who underwent DBS surgery in our unit. Different measures of targeting error were defined and compared. Analysis focused on trajectory error (TE), the closest perpendicular distance between the implanted electrode's centre and the target locus. Seventeen different demographic, clinical and procedural variables which might potentially impact accuracy were collected for each implantation. Multivariate mixed effects models were applied to identify variables significantly associated with targeting error.

Results: Mean (SD) TE for all electrodes was 1.4 (0.7) mm. There was a significant tendency for the closest point on the electrode to lie medial (0.3±0.1 mm; mean ± 95% CI), posterior (0.6±0.1 mm) and superior (0.5±0.1 mm) to the target. Three variables were independently and significantly associated with greater TE: the use of one of two identical stereotactic frames (effect size 0.4±0.2 mm), second side implantation in bilateral surgery (0.3±0.2 mm) and decreasing coronal approach angle (0.04±0.03 mm/°). All three factors were associated with significantly more posterior implantation while second side and decreasing coronal approach angle also yielded a more superiorly located point of closest approach of the electrode.

Conclusions: This is one of the only robust multivariate analyses of targeting errors in DBS surgery, identifying significant influencing factors within our workflow. We suggest that such detailed targeting error analysis should be performed routinely in each unit in order to audit targeting accuracy and identify error sources within each practitioner's individual workflow.

**77. Dr Glenn Nielsen**

The impact of COVID-19 on the Physio4FMD RCT

*Glenn Nielsen, Beatriz Santana Suarez, Ann-Marie Strudwick*

Introduction: Functional motor disorder (FMD) is a common cause of disabling neurological symptoms such as weakness and tremor. Physio4FMD is a pragmatic, multicentre single blind randomised controlled trial to evaluate effectiveness and cost effectiveness of specialist physiotherapy for FMD. Like many other studies this trial was affected by the COVID-19 pandemic.

Methods: The trial treatment of at least 89 participants (33%) was disrupted due to the pandemic. To account for this, we have extended the trial to increase the sample size. We have identified four groups based on how participants' involvement in Physio4FMD was affected; A: 25 were unaffected; B: 134 received their trial treatment before the start of the COVID-19 pandemic and were followed up during the pandemic; C: 89 were recruited in early 2020 and had not received any randomised treatment before clinical services closed because of COVID-19; D: 88 participants were recruited after the trial was restarted in July 2021. The primary analysis will involve groups A, B and D. Regression analysis will be used to assess treatment effectiveness. We will conduct descriptive analyses for each of the groups identified and sensitivity regression analyses with participants from all groups, including group C, separately.

Discussion: The COVID-19 mitigation strategy and analysis plans are designed to maintain the integrity of the trial while providing meaningful results.

**78. Dr Dimitra Nikoletou**

Impacts of Covid-19 infection and lockdown circumstances on elite student rowers

*McDonald, G., Mason, K., Nikoletou, D.*

Introduction: Elite rowers follow intense training programmes to enhance cardiorespiratory fitness and muscle power required for this highly competitive power-endurance sport. Student elite athletes have the additional pressures of academic work while competing at national and international level. The COVID-19 pandemic had a major impact on all populations but there is limited research regarding the physiological and psychological impacts of COVID-19 infection and lockdown circumstances on elite student rowers.

Aims: This study aimed to explore the impacts of COVID-19 infection and lockdown circumstances on elite student rowers.

Methods: Exploratory, qualitative design. A purposeful sample of elite student-rowers from different universities (N=14, 4M, mean age: 22.5± 2.13 years) were recruited via a social media advert on Instagram. Participants were current full or part-time students, members of a rowing club during the pandemic, competing at national level rower or above and between 18-30 years of age. Exclusion criteria were: current COVID-19 infection and underlying cardiorespiratory illness. A focus group was conducted using a topic guide and transcribed verbatim. Data were analysed using thematic analysis.

Results: Four main themes were identified: a) COVID-19 infection, with subthemes 'symptom responses' and 'return-to-training impact after infection', b) Lockdown and physiological effects, with subthemes 'changes in training routine', 'accessibility' and 'injury implications', c) Lockdown and psychological effects with subthemes 'motivation', 'coping strategies' 'athletic identity' and 'return to rowing' and d) Lockdown and support services with subthemes 'reduced access to support services', 'adaptations to management' and 'future service needs'.

Tachycardia and neuromuscular fatigue impacted athletes, causing implications for their training and return to play. Lockdown caused limited accessibility to strength equipment, coaching and physiotherapy services, resulting in training alterations and increased self-management resulting in enhanced performance results but also increased injury incidence.

Conclusion: This study highlights that elite student-rowers, who are highly motivated and well trained, were affected significantly by COVID-19 infection and lockdown circumstances in their training, performance, and well-being. Further research needs to identify the longer-term consequences of the pandemic in this population.

**79. Dr Dimitra Nikoletou**

'Partly formed out of anger…being neglected and put to one side'- End of year evaluation of a support group for people with Interstitial Lung Disease (ILD).

*Nikoletou, D., Mein, G., Conway, J.*

Introduction: Patient support groups are often developed by volunteers who have the condition themselves and often include clinical advisors in the management team. The St George's ILD support group is a patient-led group developed following an NIHR research study in pulmonary rehabilitation. Although peer support is acknowledged as valuable, there is limited evaluation of patient-led support groups in the long term.

Aims: This study aimed to explore the expectations and further needs of participants attending the St George's ILD support group a year after its creation and evaluate its effectiveness in supporting patients and carers.

Methodology: Qualitative, exploratory study. A focus group (6 patients, 2 carers and 1 clinical advisor) explored expectations and needs from support services for patients with Interstitial lung disease, experiences

of being part of a support group and suggestions for future improvements. The discussion was recorded and transcribed verbatim. Thematic analysis was used to identify relevant themes and actionable insights.

Results: Three main themes were identified: a) the long, slow and unsupported diagnostic process in ILD, b) the importance of committed and experienced health care professionals in the group and c) the need for better co-ordination of support services.

Support group participants identified that due to the long and often slow process to an interstitial lung disease diagnosis, patients would benefit from early referral to a peer-support group. The importance of experienced and committed health care professionals that input into the group, was identified as crucial for patients. There was a need for professionals to engage with the support group and maintain regular exchange of updated information. Finally, there was a request for better co-ordination of all support groups across the city to provide a more comprehensive coverage for patients and carers.

Conclusions: Support group participants agreed that their group was "partly formed out of anger… being neglected and put to one side" and were keen to persevere in improving co-ordination with health care professionals. This research highlights the need for regular evaluation and discussions with patient-led support groups in ILD to improve service provision for newly diagnosed people in this life-limiting disease.

**80. Dr Dimitra Nikoletou**

Development and evaluation of a novel, digital game, for rehabilitation in complex cardiac conditions; an exploratory, proof of concept study.

*Nikoletou, D., Dudziec, M., Bloom, V., Wang, C., Papadakis, M., Quinn, T., Makris, D.*

Background: Digital games in health have developed rapidly over the last decades but personalised games that aid rehabilitation are still underdeveloped. Our team designed a novel, non-immersive, non-contact boxing game, for exercise-based rehabilitation in people with complex cardiac conditions and comorbid breathlessness and balance problems.

Aims: This study aimed to evaluate whether cardiorespiratory and balance responses could be challenged in tandem per level of the game, to compare responses between younger and older healthy adults and to generate data for power calculations for future studies in people with cardiac conditions.

Methods: Exploratory, proof-of-concept study. 12 healthy adults (5 M), mean (SD) age 43.1 (9.7) years, played all levels of the game on a single session. The game, designed in a Microsoft Kinect platform using a 3D Game Engine (Unity), consisted of 8 levels and the player/'avatar' was required to 'box' or 'kick' bubble targets appearing in different directions. The positions and actions of the players resembled balance re-education exercises, often used in falls prevention rehabilitation programmes.

Assessments at baseline included the Timed up-and-go test (TUG), static balance (path velocity and length) using a force plate (AccuGait system) and heart rate (HR), oxygen saturation (SpO2), perceived breathlessness (BORG-10) and exertion (RPE) scores at rest. Assessments were repeated at the beginning and end of each level.

Results: Change from baseline (95 % CI) for HR, RPE, SpO2 and BORG-10 increased gradually per level. Balance responses (Path velocity and Path Length at the force platform) increased apart from levels 7 and 8 which required sit-to-stand movements. Younger and older players had similar responses to the game challenges.

Conclusion: This study demonstrated that it is possible to design a game where intensity of training, balance and perception breathlessness are challenged in tandem per level. Further research is needed to adjust and personalise this rehabilitation game and test it in people with complex cardiac disorders.

**81. Professor Pippa Oakeshott**

Is naturally occurring prebiotic Lactoferrin an acceptable alternative to antibiotic/antifungal tablets for women with bacterial vaginosis or thrush? The LISA (Lactoferrin InStead of Antibiotics/antifungals) randomised feasibility study.

*Nilofer Dayal, Pippa Oakeshott*

Background-Bacterial vaginosis and vaginal thrush/candida are common infections affecting over 200,000 women each year in England. These infections can affect sexual relationships, self-esteem, and quality of life. Recurrent vaginal infections may need repeated courses of antibiotics/antifungals which risks causing antimicrobial resistance.

Lactoferrin is a naturally occurring prebiotic protein made from milk. It is anti-inflammatory, bactericidal, and binds the iron needed for bacterial proliferation. It is present in the vagina where it helps to prevent infections and normalise the vaginal microbiome 1,2.

Aim-To see if it is feasible to conduct a future definitive trial to prove whether vaginal lactoferrin is an acceptable, effective, and cost-effective alternative to antibiotics/antifungals for women with bacterial vaginosis or thrush.

Methods- LISA is an open label randomised feasibility trial over 12-weeks in 114 women with symptomatic BV (n=57) or candida (n=57) confirmed on Gram stain. Women will be randomised 2:1 to vaginal lactoferrin or standard treatment with oral metronidazole for BV or fluconazole for candida. All women will be followed up with repeat samples and text/online questionnaires after 1,2,3,4 and 12 weeks.

Results- This study will start in 2023. In our PPI work we did an online survey of 152 women (mean age 22) with 59% response rate. 3 Most (84%) said they would be happy to try vaginal lactoferrin instead of antibiotics for BV/thrush; and 57% would be willing to provide daily vaginal samples for four weeks. We also interviewed 15 teenage female students (47% from black ethnic groups) of whom 60% said they would be interested in joining the study.

Conclusions- If this study leads to a future trial which proves that vaginal lactoferrin is an acceptable, safe, and effective alternative to antibiotics, using lactoferrin could help relieve symptoms, reduce recurrence rates, prevent antimicrobial resistance, and save NHS costs.

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**82. Dr Kazim Ogmen**

In vitro characterisation of EPHB4 variants: Mechanistic studies of EPHB4-associated Primary Lymphoedema

*Ogmen K, Martin-Almedina S, Sackey E, Grigoriadis D, Karapouliou C, Josephs K, Mortimer PS, Jeffery S, Gordon K, Mansour S and Ostergaard Pia*

Introduction: The EPHB4 gene encodes a receptor tyrosine kinase protein, EPHB4, that binds to its ligand EphrinB2, to initiate complex contact-dependent bidirectional signalling cascades, controlling cellular fate during embryonic angiogenesis and essential cellular processes such as adhesion, migration, and proliferation, in both blood and lymphatic endothelial cells. Recently, EPHB4 kinase-inactivating mutations have been associated with primary lymphoedema and autosomal dominant susceptibility to nonimmune hydrops fetalis.

Although, EPHB4 mutations have been found causative in lymphatic-related diseases, the mechanism responsible for disease causing phenotype needs more attention for possible future therapeutics.

Objective: The impact of EPHB4 mutations on lymphatic system are not well understood. Therefore, it is crucial to understand downstream cellular signalling and functional roles of EPHB4 in lymphatic systems.

Methods; WES and Sanger sequencing analysis identified 7 novel variants in EPHB4. Functional analysis of the variants was performed in Primary human dermal lymphatic endothelial cells (LECs) by either overexpressing EPHB4 variants or RNAi knockdown. Investigations were carried out to study protein function and downstream signalling (Western blot, Immunoprecipitation and Immunofluorescence), and the role of EPHB4 function in VEGF-C-driven lympangiogenesis (spheroid-based sprouting assays).

Conclusions; Functional analysis of different variants in EPHB4 demonstrated high heterogeneity, showing a spectrum of dysfunctional mechanisms, from total loss of protein expression to normal levels of expression and normal localization but reduced activity. Also, EPHB4 appears to be an important regulator of proliferation and angiogenesis in lymphatic endothelial cells. Our results indicate different molecular mechanisms causing EPHB4-related pathogenesis and urge for a better understanding of the role of EPHB4 forward and reverse signalling in the function of the lymphatic and vascular systems.

**83. Professor Christopher Owen**

Non-Pharmacological Interventions to Lengthen Sleep Duration in Healthy Children A Systematic Review and Meta-Analysis

*Magee L, Goldsmith LP, Chaudhry UAR, Donin AS, Wahlich C, Stovold E, Nightingale CM, Rudnicka AR, Owen CG*

IMPORTANCE Adequate sleep duration is necessary for many aspects of child health, development and wellbeing yet sleep durations for children are declining, and effective strategies to increase sleep in healthy children remain to be elucidated.

OBJECTIVE To determine whether non-pharmaceutical interventions to improve sleep duration in healthy children are effective, and to identify the key components of these interventions.

DATA SOURCES CENTRAL, MEDLINE, Embase, PsycINFO, Web of Science Core collection, ClinicalTrials.gov, and WHO trials databases were searched from inception to 15th November 2021.

STUDY SELECTION Randomised controlled trials of interventions to improve sleep duration in healthy children were independently screened by 2 researchers. A total of 28,478 studies were identified.

DATA EXTRACTION AND SYNTHESIS Data were processed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Random effects meta-analytic models were used to estimate pooled effect sizes.

MAIN OUTCOME AND MEASURE The outcome was difference in sleep duration measured in minutes.

RESULTS Pooled results indicate that sleep interventions (45 trials, n=13,539) were associated with 10.5 minutes (95%CI, 5.6 to 15.4) longer nocturnal sleep. There was substantial variation between trials. Sources of variation that were not associated with the study effect size included age group, whether the population was identified as having a sleep problem or being disadvantaged, method of assessment of sleep duration (objective versus subjective), location of intervention delivery (home versus school), whether interventions were delivered in person, used parental involvement, behavioural theory, environmental change, or had greater or lower intensity. Interventions that included earlier bedtimes were associated with a 47-minute sleep extension (3 trials, 95%CI 18.9 to 75.0), compared with remaining studies (42 trials, 7.4 minutes 95%CI 2.9 to 11.8; p=0.006 for group difference). Trials of shorter duration (<6 month) had larger effects.

CONCLUSIONS AND RELEVANCE Interventions focussed on earlier bedtimes may offer a simple, pragmatic, effective way to meaningfully increase sleep duration that could have important benefits for child health.

**84. Mr Davide Radaelli**

Sudden Cardiac Death in Adolescents: Insights from a Large United Kingdom Registry

*Finocchiaro G.; Radaelli D.; Papadakis M.; Behr E.; Sharma S.; Westaby J.; Sheppardb M. N.*

Background and aims: Causes and precipitating factors of sudden cardiac death (SCD) in adolescents are poorly understood. The aim of the study was to investigate the causes of SCD and their association with intensive physical activity in a large cohort of adolescents in a large national database.

Methods: Between 1994 and 2022, 7675 cases of SCD were consecutively referred to our national cardiac pathology centre; 756 (10%) were adolescents (age 16±2 years, 69 % males, 74% Caucasian, 4% Afro-Caribbean). All subjects underwent detailed post-mortem evaluation including histological analysis by expert cardiac pathologists. Clinical information, including athletic status, was obtained from referring coroners and entered into database.

Results: A structurally normal heart, indicative of sudden arrhythmic death syndrome (SADS) was the most prevalent autopsy finding (n=474, 63%). Myocardial diseases were detected in 163 (22%) cases, including arrhythmogenic cardiomyopathy (AC) (n=36; 5%), hypertrophic cardiomyopathy (HCM) (n=31; 4%), idiopathic left ventricular hypertrophy (LVH) (n=31; 4%) and myocarditis (n=30; 4%). Coronary artery anomalies were identified in 17 (2%) cases while congenital heart disease and/or valve disease were identified in 44 cases (6%). Decedents were athletes in 128 (17%) cases; 159 (21%) decedents died during exercise. SADS was less common in athletes (52%) compared to non-athletes (65%), p<001; AC was diagnosed in 8% of athletes compared with 4% of non-athletes, p=0.05 while myocarditis was exclusively found in non-athletes (5% of the cases, p<0.001). Coronary artery anomalies were significantly more common in athletes (9% vs 1%, p<0.001). Commotio cordis was more common in athletes (5% compared to 1% in non-athletes, p=0.001). The three main comorbidities were asthma (n=58; 8%), epilepsy (n=44; 6%) and obesity (n=40; 5%).

Conclusions: SADS and myocardial diseases are the most common conditions predisposing to SCD in adolescents. Prevalence of certain conditions such as arrhythmogenic cardiomyopathy, coronary artery anomalies and commotio cordis is higher in young athletes who died suddenly.

**85. Ms Madeleine Rossanese**

Investigating platelet regulation of matrix metalloproteinase expression in monocytes during Mycobacterium tuberculosis infection

*Rossanese, M.E., Kirwan, D.E., Skolimowska, K.H., Kutschenreuter, J., Cusman, R., Chong, D.L.W., Friedland, J.*

Mycobacterium tuberculosis (M. tb) complex bacteria are historically humanity's deadliest pathogens, responsible today for approximately 1.5 million deaths each year. Tuberculosis disease has left 155 million living survivors with a wide spectrum of costly lifelong morbidities, largely due to the extensive lung tissue destruction that characterizes pulmonary tuberculosis. Monocytes have been identified as a key immune cell in this tissue destruction through their immune effector functions, particularly the secretion of enzymes called matrix metalloproteinases (MMPs). This project aimed to investigate the mechanisms by which platelets may regulate the monocyte immune response to infection with M.tb. I optimized a heterologous in vitro monocyte and platelet co-culture system to establish an immune phenotype to M. tb infection, which was further explored using cell-signalling protein inhibitors. I measured monocyte secretion of MMP-1, a key collagenase which drives lung tissue degradation, by ELISA and investigated the phosphorylation state of specific cell signalling molecules implicated in pathways regulating monocyte MMP-1 secretion by Western blot. I was able to demonstrate firstly that platelets augment monocyte secretion of MMP-1 following infection with M. tb;

and secondly, that platelets use the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3?-kinase (PI3K) cell signalling pathways within monocytes to exert this influence. These data are consistent with and drive forward work previously conducted both within and outside my group and may help to elucidate some of the niches in which there are opportunities to deploy host-directed therapies for the prevention and mitigation of uncontrolled lung tissue damage during M. tb disease.

**86. Professor Alicja Rudnicka**

Artificial intelligence enabled retinal vasculometry for prediction of circulatory mortality, myocardial infarction and stroke

*Alicja R Rudnicka PhD,1 Roshan A Welikala PhD,2 Sarah A Barman PhD,2 Paul J Foster PhD,3,4 Robert Luben PhD, 3,5 Shabina A Hayat PhD,6 Kay-Tee Khaw FRCP,5 Peter H Whincup PhD,1 David P Strachan MD,1 Christopher G Owen PhD 1, on behalf of the UK Biobank Ey*

Aims: Population screening for MI and stroke using risk prediction tools exist but have limited uptake; currently risk scores for circulator mortality do not exist. We examine whether inclusion of Artificial Intelligence (AI)-enabled retinal vasculometry (RV) improves existing risk algorithms for incident stroke, myocardial infarction (MI) and circulatory mortality.

Methods: AI-enabled retinal vessel image analysis processed images from 88,052 UK Biobank (UKB) participants (aged 40-69 years at image capture) and 7,411 EPIC-Norfolk participants (aged 48-92). Retinal arteriolar and venular width, tortuosity and area were extracted. Prediction models were developed in UKB using multivariable Cox proportional hazards regression for circulatory mortality, incident stroke and MI, and externally validated in EPIC-Norfolk. Model performance was assessed using optimism adjusted calibration, C- and R2 statistics. Performance of Framingham risk scores (FRS) for incident stroke and incident MI, with addition of RV to FRS, were compared with a simpler model based on RV, age, smoking status and medical history (antihypertensive/cholesterol lowering medication, diabetes, prevalent stroke/MI).

Results: UKB prognostic models were developed on 65,144 participants (mean age 56.8; median follow-up 7.7 years) and validated in 5,862 EPIC-Norfolk participants (67.6, 9.1 years respectively). Prediction models for circulatory mortality in men and women had optimism adjusted C- and R2 statistics between 0.75-0.77 and 0.33-0.44 respectively. For incident stroke and MI, addition of RV to FRS did not improve model performance in either cohort. However, the simpler RV model performed equally or better than FRS.

Conclusion: AI-enabled RV extraction offers a non-invasive prognostic biomarker of vascular health that does not require blood sampling or blood pressure measurement, and potentially has greater community reach to identify individuals at medium-high risk requiring further clinical assessment. Retinal imaging cameras are used routinely in high-street opticians and could provide an alternative risk assessment pathway to promote attendance in primary care for cardiovascular clinical assessment and management.

**87. Mrs Ege Sackey**

A Novel causative gene for Autosomal Dominant Primary Lymphoedema (PL)

*Sackey E, Ogmen K, Martin-Almedina S, Moy R, Grigoriadis D, Dobbins S, Mansour S, Gordon K, Keeley V, Birdsey G, and Ostergaard P*

Primary lymphoedema is caused by abnormal development of lymphatic vessels or failure of lymphatic function due to genetic abnormality. To date, the genetic causes of around 70% of PL cases are still waiting to be discovered. Through 100,000 Genomes Project (100KGP) whole genome sequencing and in-house exome sequencing data, four frameshift and 2 nonsynonymous mutations in ERG were identified. These variants have not been found in either the 100KGP control group (~78K) or the gnomAD database.

Co-segregation analyses were performed by Sanger sequencing for four of the variants. Followingly, functional validation of the variants was performed. Human dermal lymphatic endothelial cells (HDLECs) were transfected with pcDNA3 expression plasmid for ERG wildtype and ERG variants and Western blotting and immunofluorescences were used to observe the protein expression levels and cellular localization of the protein. Pathogenicity was demonstrated in all variants investigated. Reduction or loss of protein production and aberrant subcellular localization was observed.

ERG is a critical transcriptional regulator of blood vessel endothelial cell (EC) gene expression and ERG expression in ECs is studied in detail, and it is shown to be essential for normal vascular development. Even though its involvement in angiogenesis and haematopoiesis is well known there is limited information about the contribution of ERG to lymphatic development or how the variants identified to lead to primary lymphoedema. However, co-localisation of ERG in lymphatic vascular structures in the mouse ear and high levels of ERG expression in the lymphatic endothelium have been observed. Further research is necessary to understand the exact disease mechanism of the identified variant.

To conclude, novel mutations in ERG appear to be pathogenic and are likely to cause autosomal dominantly inherited primary lymphoedema.

**88. Dr Anna Sadnicka**

Postural instability in DYT-TOR1A dystonia dynamically dependent on sensory feedback

*Anna Sadnicka, Elena Dennis, Kailash Bhatia, Scott Albert, Reza Shadmehr, John Rothwell, Joe Galea*

Dystonia is a hyperkinetic movement disorder in which there is an abnormality of postural control. In this study we put the spotlight on the neural control of sustained hold and examined the influence of visual and proprioceptive feedback over performance.

Ten patients with DYT-TOR1A dystonia and 30 controls held the handle of a planar robotic arm to make point-to-point reaching movements with their symptomatic right arm. Reaches were made from a central start box to eccentric targets (15°, 135°, 225° or 315°). Position was then held within the target box for 10s. Estimation of arm position was dependent on proprioceptive and visual feedback (experimentally manipulated with balanced pseudo-randomization: cursor visible or not visible).

In patients, sustained hold was interrupted by movements with discrete velocity peaks. Such fluctuations were not seen in controls during sustained hold and were present in both feedback conditions in dystonia. Interestingly by the end of the hold phase accuracy performance segregated; with visual feedback (high accuracy, low variability, performance in line with controls); with no visual feedback (low accuracy, high variability, significant deficits compared to controls).

Our results reveal the instability of hold in dystonia and the dynamic dependence on sensory feedback. These findings help to explain clinical features, offer insight into neural control mechanisms and inform future therapeutic strategy.

**89. Dr Eleftherios Samaras**

Investigating the relationship between power, behaviour and hubris

*Samaras E., Giosanu I., Ydler G., Worthy B., Vidal L., Sollazzo G., Akstinaite V., Vidal M-E., Garrard P*

People who achieve significant power run the risk of succumbing to its proverbially corrupting tendencies, and developing dangerous, ultimately destructive, behaviours. The striking uniformity of this phenomenon led former Foreign Secretary David (Lord) Owen and the American psychiatrist, Jonathan Davidson to formulate the problem in medical terms, using the concept of a 'disorder of power', which they termed the 'Hubris

syndrome' (HS). This study aims to identify ~500 individuals who held power across different occupational categories in the 20th Century. As well as personal and biographical characteristics, data relevant to changes in behaviour and language, and the specific events preceding these changes will also be of interest. Subjects are selected a) from different leadership domains (politics, business, the military, religion, and the professions (including teaching, medicine and the law)); and b) according to the organisational impacts of their leadership careers (positive or negative). Data can be harvested from online information resources, and from print and broadcast media if available. The study uses knowledge graph methodology to represent the multiple factors - including developmental, educational, behavioural, and experiential - and their interplay, that influence powerful people's development or avoidance of HS. Machine learning is used to identify the factors that predispose to or protect from this destructive behavioural phenomenon.

**90. Dr Shari Sapuan**

The distribution and determinants of human cytomegalovirus (HCMV) shedding in HCMV-seropositive women during pregnancy

*Sapuan, S. Tan, NK. Carrington, D. Greening, V. Jones, CE. Parsons, R. Pope, CF. Strang, B. Heath, PT.*

Human cytomegalovirus (HCMV) may be detected in bodily fluids, known as shedding, of pregnant women previously infected with HCMV, known as being HCMV-seropositive, which may then suggest a non-primary maternal infection. The association between HCMV shedding in HCMV-seropositive pregnant women and the vertical transmission of HCMV to their unborn child to result in congenital infection, is poorly investigated. We aimed to assess the distribution and determinants of HCMV shedding in HCMV-seropositive women during pregnancy.

Healthy HCMV-seropositive pregnant women with young children, receiving antenatal care in St George's Hospital, London, were recruited at the beginning of their pregnancy. Over three time-points in pregnancy (beginning, middle, end), saliva, urine, and vaginal secretion samples were tested for HCMV DNA using PCR, and blood samples were tested with two HCMV interferon gamma release assays: ELISPOT and QuantiFERON. Using questionnaires, details on sociodemographic were collected at the beginning, and details on hygiene-related contact with their young children's saliva and urine were collected at each time-point of sample collection.

122 HCMV-seropositive women were recruited. The prevalence of HCMV shedding detection at any time-point in pregnancy was 22.1% [95% CI: 15.0,30.3] (27/122) in any bodily fluid, 3.3% [95% CI: 0.9,8.1] (4/122) in saliva, 13.0% [95% CI: 7.6,20.3] (16/122) in urine, and 16.4% [95% CI: 10.2,24.0] (20/122) in vaginal secretions. There was no significant difference in the outcome of HCMV shedding during pregnancy based on sociodemographic, on hygiene-related contact with their young children's saliva and urine, and on HCMV-specific cellular mediated immunity (CMI) as measured by the HCMV-QuantiFERON assay. The HCMV-ELISPOT spot count to pp65 antigen was lower when HCMV shedding was detected, significantly so at the second time-point.

The fact that exposure to young children's bodily fluids which may increase the women's exposure to different HCMV strains, was not found to be associated with HCMV shedding, may suggest that the shedding seen is due to reactivation of existing HCMV strain: genome sequencing work may be useful to explore this hypothesis further. HCMV-specific CMI to pp65 antigen, as assessed with a HCMV-ELISPOT assay, may be important in the prediction and control of HCMV shedding in HCMV-seropositive pregnant women.

**91. Miss Isabel Schiavi**

Diverse growth phenotypes of BCG Pasteur induce variation of Vγ9Vδ2 T cell activation

*Schiavi, I, Ridgley, L, Bodman-Smith, M, Bull, T*

Background: γδ T cells constitute between 0.5-10% of T lymphocytes in human peripheral blood. They behave like an innate and adaptive immune cell and have therefore been coined as 'adaptate'. Vγ9Vδ2 T cells are indirectly activated by phosphoantigens (pAgs) such as endogenous isopentenyl pyrophosphate (IPP) and exogenous/bacterial (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP). IPP and HMBPP are metabolites of eukaryotic and prokaryotic pathways respectively and are responsible for isoprenoid biosynthesis, activating Vγ9Vδ2 T cells through interaction with a butyrophilin molecule (BTN3A1) on target cells. It has previously been shown that mycobacteria such as Bacillus Calmette-Guérin (BCG) activate Vγ9Vδ2 T cells through this mechanism resulting in their ability to kill tumour cells via direct or indirect mechanisms.

Methods: BCG Pasteur was grown under different conditions to induce varying phenotypes. These phenotypes were then used in an activation assay to determine specific activation and expansion of Vγ9Vδ2 T cells. PBMC cells were stained with fluorescent antibody surface markers, measured using flow cytometry and gated according to cell populations of interest.

Results: The most activating BCG Pasteur phenotype was found to be 'cording', whereby it expressed higher activation markers (CD25 and HLA-DR) compared to both 'clumpy' and 'homogenous' BCG phenotypes. CD69 expression in the 'cording' phenotype reached maximum within 24 hours, whereas the 'clumpy', 'homogenous' and positive control reached maximum at 72 hours. Importantly, these activation profiles are unique to Vγ9Vδ2 T cells.

Conclusions: This preliminary data provides exciting evidence to show how phenotypically different BCG induce varying Vγ9Vδ2 T cell responses.

**92. Mr Stephen Smith**

Endotrachal tube placement; a comparison between pre-hospital services and a London major trauma centre.

*Smith, S.*, *Hudson, A*

The incorrect placement of an endotracheal tube during intubation has been associated with serious complications including hypoxia and pneumothorax. Previous studies have indicated that when performed in-hospital, endotracheal tubes are more likely to be inserted to the appropriate depth than pre-hospital. The primary objective of this investigation was to measure how frequently intubation tubes were inserted to the correct depth at St George's Emergency Department (ED) in the year 2021 in comparison with Ambulance, HEMS, and other health care services. A secondary objective of this study was to evaluate the time to and from intubation to a Computerised Tomography (CT) scan assessment of the endotracheal tube depth. To achieve these objectives, a retrospective case analysis of 152 patients with endotracheal tube placement through St George's ED in 2021 was conducted, and intubation was graded as satisfactory, too deep, or too shallow based on their CT imaging. The most significant finding was that pre-hospital intubations had a satisfactory positioning rate of 92.3% compared to the in-hospital satisfactory positioning rate of 82%. Additionally, the mean time to CT was 36 minutes and only 1 endotracheal tube was placed too shallow, which was in-hospital. The reasoning behind why the results of this investigation differed from previous data are unclear. However, the finding that pre-hospital services are accurately placing endotracheal tubes in the vast majority of cases where imaging isn't immediately available is reassuring. However, in cases where there is a delay to CT, we suggest an immediate chest x-ray post-intubation or on arrival in hospital to check tube position.

**93. Miss Ananya Sood**

Finding a leg to stand on: reconceptualising the place of arts and humanities within medical education

*Ananya Sood (1,2) Matt Bates (3) Deborah Padfield (1,4) Annie Bartlett (1) Jo Winning (3)*

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Instigated as a challenge to C.P. Snow's much-contested 'two cultures' pronouncement, the undergraduate module: Finding a Leg to Stand On: Clinical, Cultural and Creative approaches to the Human body introduces an innovative transdisciplinary model for bringing humanities and healthcare education together. Co-taught by clinicians, academics and artists it asks: what new learnings might emerge from bringing humanities students into hospital settings and medical students into humanities classrooms and from exchanges where students and staff learn from each other?

A transdisciplinary student cohort was created from healthcare students attending St Georges, and humanities students from Birkbeck, University of London. The 'leg' was used as a vehicle through which to examine the human body via medical, critical & cultural theory and creative practice. The module included: two-hour weekly sessions over 11 weeks, in-depth analysis and discussion of diverse disciplinary texts, collaborative writing and drawing exercises, museum and clinical environment visits, regular ten-minute movement workshops and group reflective writing at the end of each session.

Student feedback (n=20) evidenced the approach broadened their learning experience: 85% believed their thinking had changed as a result of the transdisciplinary learning; 80% asserted their own disciplinary understandings, across a wide range of disciplines, had been positively enhanced, 90% considered reflective writing practice was useful and 80% relished the movement exercises.

The approach responded to an appetite to find new ways of: embedding the arts and humanities within healthcare training, encouraging collaboration between staff and students, supporting a democracy of discourse and replacing external critique of clinical practice with a collaborative opening-up and reimagining of all things clinical. Supporting five of the sixteen General Medical Council outcomes for graduates, the external examiner rated the module as 'an exemplary, flagship course that is the epitome of excellence in higher education'.

As recently as August 2021, Nicholas Dirks, suggested that 'the perpetuation of the two cultures, delineated by Snow is still very much present on college campuses.' As our individually-reimagined Venn diagrams shows, we strongly contest the 'two cultures' model and offer an alternative vision of the relationship between the humanities disciplines and training and delivery of healthcare.

Reference:Nicholas Dirks, 'The "two cultures" must finally be reconciled', Times Higher Education Supplement, August 5th 2021

**94. Miss Yasmin Taghvaipour**

Does teaching anatomy online with 3D digital models enhance student's learner gain and satisfaction as compared to 2D images?

*Bhate, R., Haddad, N., Zazai, R., Hayes, J., Taghvaipour, Y., Holmes, C.J., Dadali, A., Longhurst, G.,*

The Covid-19 pandemic has accelerated the use of 3D digital models in anatomy education. Many universities have purchased 3D software packages to compensate for the closure of their dissection rooms. Despite their increased usage, the educational advantage and degree of student satisfaction of 3D digital models remains under evaluated when compared to 2D images such as illustrations and diagrams to teach anatomy. The

primary aim of this study was to compare student satisfaction and learner gain of 3D versus 2D visualisation tools using the Kirkpatrick model of evaluation. The

secondary aim was to assess if teaching anatomy online using these visualisation tools translates into a true interpretation of cadaveric images. Students studying medical sciences (n=173) were randomly allocation into tutorial groups utilising either 2D or 3D visualisation tools. These tutorials were led by peer-tutors and covered a range of anatomical regions. Likert-scale questionnaires were used before and after the tutorial to evaluate student satisfaction. Learner gain was calculated from pre- and post-tutorial test scores, based on cadaveric image-based questions. To determine if utilising 2D and/or 3D resources directly translates into understanding of cadaveric

images, the post-tutorial test contained five questions from the pre-tutorial test, and seven supplementary questions previously unseen by the participants. Students in both groups responded positively to all levels of the Kirkpatrick model. After the tutorials, 100% (2D group) and 83% (3D group) agreed that satisfaction would be higher if 3D models were incorporated into

teaching. Students correctly answered 53.01% and 55.49% of the supplementary question after the 3D and the 2D tutorials, respectively. No significant difference in the learner gain was found between the 3D (+0.11) and 2D (+0.17) groups. Our results report that student satisfaction is higher

when 3D digital models are incorporated into teaching anatomy online. However, their use doesn't necessarily result in an education advantage over 2D visuals. In conclusion, the use of 3D digital models might not always be intellectually stimulating despite of their admired visual appeal. This

study was given a favourable ethics opinion by St George's, University of London Research Ethics Committee (ref. number - 2021.0082).

**95. Mr Adil Terracciano**

The Epidemiology of Paediatric Distal Forearm Fractures

*Terracciano, A., Rupra, R.,Parmar, S., Leitch, P., Asirvatham, RD.,Gelfer, Y., Yeo, A., Hing, CB.*

Aim: 40-50% of children in the UK experience a fracture in their lifetime, accounting for 9% of annual paediatric A&E presentations. Few studies have focussed on paediatric fracture incidence and temporal trends. This study investigated trends in paediatric forearm fractures over a 7-year period at a level 1 inner city trauma centre to identify at risk populations.

Method: Data were collected retrospectively from St Georgeâ€™s Hospital on all children presenting with a suspected distal forearm fracture between 5th September 2012 and 26th June 2019 (n=4702). Radiologist reports of radiographs were used to assess for a fracture. Patient demographics and admission data were collected from electronic patient records.

Results: 2097/4702 (44.6%) patients were found to have a new fracture, 1332 (64.4%) were male. Patients were most commonly aged 8-11 years on presentation (759/2097) and 1057 (50.4%) were Caucasian. In total 48.0% of fractures were sustained during sport, most commonly football (450/1005). The incidence of distal forearm fractures in children more than doubled from 192 to 402 across 2013-2018.

Conclusions: The incidence of paediatric distal forearm fractures is increasing with time resulting in an increased burden on resources. Improved prevention measures could limit injury in higher risk groups such as boys of primary school age that play football.

**96. Ms Oanh Tran**

Development and optimisation of genetically encoded calcium sensors

*Tran O., Hughes H., Carter T., Török K.*

Abnormal calcium signalling has been observed in several human diseases such as myopathies, Alzheimer's disease and cancers. Genetically encoded calcium sensors are powerful tools to monitor calcium ion transients which will help to understand human diseases. This task requires calcium sensors to have high brightness and fast kinetics.

Several generations of calcium sensors have been developed based on circularly permutated fluorescent protein (cpEGFP) and the calcium binding-induced interaction of calmodulin and a peptide. The latest generation of such sensors is jGCaMP8f (Zhang et al., 2020).

In jGCaMP8f, in the absence of calcium, calmodulin and its binding domain derived from nitric oxide synthase (eNOS) are not bound to each other which leaves the constituent circularly permuted EGFP (cpEGFP) in a low fluorescence state due to a cut in one of the beta-strands that form the beta-barrel structure of EGFP. In the presence of calcium, calcium/calmodulin is formed which strongly associates with the eNOS peptide. Their interaction repairs the defect in the beta-barrel structure leading to an enhanced fluorescent state. The tight binding between calcium/calmodulin and the eNOS peptide facilitates the enhancement in fluorescence, however it also causes the complex to have a slow dissociation rate when calcium is removed.

jGCaMP8f has moderate brightness and fluorescence dynamic range (7-fold calcium induced fluorescence increase), and its calcium decay rate is only approximately 30 s-1(at 20oC).

To improve the properties of jGCaMP8f, we hypothesized that mutations in the calcium binding sites of calmodulin and/or in the eNOS peptide of jGCaMP8f will weaken the binding affinity resulting in faster calcium off-kinetics. In turn, mutations that stabilise the calcium/calmodulin – eNOS peptide binding may increase the brightness and fluorescence dynamic range (the fluorescence enhancement that occurs upon calcium binding). Two improved variants are presented: jGCaMP8f L27A which has a 3-fold faster off-kinetics and jGCaMP8f F366H which shows a 3-fold greater dynamic range than jGCaMP8f, both in vitro and in HEK293T cells in response to ATP stimulation. We propose that our novel faster and brighter jGCaMP8f variants will be useful tools for studying calcium signalling in health and disease.

**97. Miss Zoe Tryfonos**

Regulation of Placental Vascular Development in the First Trimester of Pregnancy

*Tryfonos, Z., Whitley, GStJ., Charolidi, N., Frick, A., Ashton, S., Bodman-Smith, M., Dumitriu, IE and Cartwright, JE.*

Pre-eclampsia is a complication that affects 3-8% of pregnancies globally and is one of the leading causes of maternal mortality. Despite the severity and prevalence of the condition, the underlying cause is yet to be identified. Hofbauer cells (HBC) are fetal macrophages located in the placenta, but their function is yet to be determined. We propose that HBC are regulators of placental vasculature development in the first trimester of pregnancy. Uterine artery Doppler Ultrasound scanning can be used to identify first-trimester pregnancies at a higher risk of developing pre-eclampsia, had the pregnancy continued to term. We aimed to investigate whether there were underlying differences between placentas from pregnancies at a higher risk of developing pre-eclampsia compared to those with a normal risk, determined by Doppler ultrasound. To explore this, we imaged and analysed the structure of the first-trimester placental vasculature using wholemount immunofluorescence and confocal microscopy. We found no significant differences between the high and normal risk groups when comparing the average vessel length, number of branch points, and volume of the tissue occupied by vessels. This led us to investigate cellular and molecular differences. We optimised isolation methods to obtain pure populations of both endothelial and HBC from placental tissue and found that

endothelial cells from pregnancies at a higher risk of developing pre-eclampsia are more sensitive to apoptotic stimuli. Moreover, we designed a flow cytometry panel and Luminex panel to characterise HBC. We found that HBC express a range of markers across the macrophage polarisation spectrum, suggesting they may have tissue-specific roles in the placenta. Analysis of secreted factors from HBC by Luminex assay suggest that HBC function in regulating the behaviour of neighbouring vascular cells by secreting factors such as VEGF, an important regulator of angiogenesis. Using the conditioned media from HBC cultures, functional assays were carried out to evaluate how HBC could influence endothelial cell behaviours, such as cellular apoptosis, motility, proliferation, activation, and angiogenesis. To conclude, our findings suggest that HBC play a role in regulating endothelial cell behaviour and may, therefore, contribute to the development of the placental vasculature in the first trimester of pregnancy.

**98. Miss Brianna Watson**

The Importance of Receptor Signalling Crosstalk in Platelets

*Brianna Watson, Iain A Greenwood, James TB Crawley and Isabelle I Salles-Crawley*

Platelets are anucleate cells that play a significant role in haemostasis and thrombosis. Whilst normal platelet function is vital in preventing excessive blood loss, dysregulated platelet activation can result in fatal thrombotic pathologies such as myocardial infarction, stroke and venous thromboembolism. Glycoprotein (GP) Ib? and GPVI are two key platelet surface receptors involved in platelet activation. We have recently demonstrated that the intracellular domain of GPIb? plays a role in GPVI mediated signalling events. The aim of this project is to underpin the molecular mechanisms of this receptor crosstalk.

GPIb?+/+ (WT) and GPIb??sig/?sig platelets were stimulated with a GPVI specific agonist - collagen related peptide (CRP) and lysed at different timepoints following stimulation. Phosphorylation levels of GPVI-mediated signalling molecules were measured by western blots. Recombinantly expressed GPIb? intracellular domains were expressed in BL21 bacterial cells: a wild-type recombinant protein, one with Ser587Asp/Ser590Asp/Ser609Asp phosphomimetic substitutions to mimic activated GPIb? and one with the last 24 amino acids truncated.

Upon CRP stimulation, phosphorylation levels of LAT (Linker for the Activation of T cells) which signals downstream of GPVI, was significantly reduced in GPIb??sig/?sig platelets compared to WT platelets while LYN (a Src-family tyrosine kinase) phosphorylation levels remained unchanged. Lastly, early work on the expression of recombinantly expressed GPIb? intracellular tails showed that all three proteins were successfully expressed after 4-24 hours IPTG stimulation.

The next steps of the project will be the large-scale expression and purification of the GPIb? recombinant proteins. These recombinant proteins will be conjugated to magnetic beads and pull-down assays using human platelets will be performed. Alternatively, GPIb? from human platelets will be immunoprecipitated with anti-GPIb?-antibody-conjugated beads to identify receptors/proteins associated with GPIb?. Pull-down samples will be analysed by SDS-PAGE and sent for mass spectrometry analysis. We are also currently investigating phosphorylation levels of additional GPVI-mediated signalling molecules (e.g. FcR?, SRC kinases and Btk) in CRP stimulated GPIb??sig/?sig and WT platelets to further understand how the deletion of the GPIb? intracellular domain impacts upon GPVI/collagen signalling. This may identify novel therapeutic targets for more effective antiplatelet drugs for the treatment of cardiovascular disease.

**99. Ms. Zena Wehbe**

Sex-dependent differences in the functionality of a novel smooth muscle relaxant

*Zena Wehbe, Iain A. Greenwood*

Introduction: By 2018, 72% of randomized controlled clinical trials of new drugs lacked any analysis of sex-dependent differences. Consequently, most medications have been prescribed at the same dose for males and females, resulting in women being 75% more likely to display an adverse drug reaction compared to males. We suggest that this discrepancy is attributed to differences in the expression, regulation and trafficking of the molecular targets of many of these drugs. As such, it is warranted to evaluate the function and the target of novel drugs in both sexes even before clinical trials. With regards to this, a novel pharmacological modulator of voltage gated potassium (Kv7) channels has been developed for initial testing and sex-dependent considerations should be included in its analysis. In smooth muscle cells, activation of Kv7 channels induces repolarization and subsequent relaxation, thereby representing a promising therapeutic target to treat smooth muscle disorders related to hypercontractility, like overactive bladder. We hypothesize that targeting Kv7 channels with a novel drug, Kb1754, will repolarize the membrane of smooth muscle cells and that its effect may vary between the sexes. We aim to specifically characterize the effect of Kb1754 using the detrusor smooth muscle of the bladder and to evaluate sex differences in the expression, function and trafficking of its target Kv7 channel.

Methods: Strips of bladder from male and female Wistar rats were mounted in a 4 chamber myograph. To characterize the functional effect of Kb1754 on the strips, isometric tension studies were conducted, including concentration, time and sex-dependent effects. qPCR was used to evaluate transcript expression of Kv7 (kcnq) channels, their beta accessory KCNE (kcne) subunits, and their regulatory membrane trafficking protein dynein (dlc-1).

Results and Conclusions: Kb1754 relaxed bladder strips in a dose dependent manner. The drug exerted significantly greater relaxation in bladders from males compared to females and the effect was estrous cycle dependent. Q-PCR revealed differential expression of kcnq, kcne and dlc-1 in bladders from male and female rats. The results thus far illustrate a promising therapy for overactive bladder, while also highlighting sex differences in the response to the drug.

**100. Dr Joseph Westaby**

Obesity cardiomyopathy in sudden cardiac death: A distinct entity? An observational case control study.

*WESTABY, JD, DALLE-CARBONARE, C, JOHNSON, D, CHIS STER, I, MILES, C, MEIJLES, D, PAPADAKIS, M, BEHR, ER, SHEPPARD, MN.*

Background: Obesity has reached epidemic proportions affecting 13% of the world's population and is associated with coronary disease, diabetes and hypertension. Obesity cardiomyopathy (OCM), cardiomegaly and cardiac dysfunction in the absence of these and other causes, is increasing in incidence.

Methods: 6457 sudden death cases were referred to our cardiovascular centre between 1994 and 2020. OCM was identified by an increased heart weight (>550g in males and >450g in females) in obese individuals (BMI?30) in the absence of pathological evidence of ischaemic disease, valvular disease or other causative aetiology as well as clinical evidence of hypertension or diabetes. Cases were sex and age matched to obese and normal weight controls (18.5?BMI?24.9) with a morphologically normal heart.

Results: The odds ratio of cardiomegaly for obese individuals compared to healthy weight individuals was 5.3 (2.9-9.6, p<0.001). Mean age at death of 53 individuals with OCM was 42±12 with a male predominance (n=34, 64%). Death occurred predominantly at rest (48, 91%) without preceding symptoms (46, 87%). Males died younger than females (40±13 vs 45±10, p=0.036). BMI was increased in OCM cases compared with obese controls (41.9±8.4 vs 34.6±4.0). Average heart weight was 598±93g. There were increases in right and left

ventricular muscular wall thickness (all p<0.05). Right ventricular epicardial fat was increased compared to healthy weight controls only. Left ventricular fibrosis was identified in 7 (13%) cases.

Conclusions: OCM is a specific pathological entity associated with sudden cardiac death. It is seen in males at a younger age and with increased BMI. We propose diagnostic criteria of cardiomegaly (>550g in males and >450g in females) in individuals with a BMI>30kg/m2 in the absence of hypertension or other aetiology for a diagnosis at post mortem.

**101. Dr Sarah White**

What implementation factors are predictive of engagement with peer support? A secondary analysis of a randomised controlled trial of one-to-one peer support for discharge from inpatient psychiatric care

*White, S. Bhattacharya, R. Bremner, S. Faulkner, A. Foster, R. Gibson, S. Goldsmith, L. Hartnett, D. Patel, A. Priebe, S. Repper, J. Rinaldi, M. Salla, A. Simpson, A, Ussher, M. Gillard, S.*

Background: A range of evidence for the effectiveness of one-to-one peer support in mental health services is emerging. Levels of engagement with peer support vary with limited studies showing few individual participant characteristics predicting engagement. Implementation factors that might predict engagement have not been considered.

Methods: This study aims to examine the following implementation factors as possible predictors of engagement; receiving at least two peer worker contacts on the ward; peers and peer workers having similar characteristics with respect to age, gender, ethnicity, diagnosis; length of first contact; days between recruitment and discharge; number of relationship building activities in first contact. It is a secondary analysis of the ENRICH trial of one-to-one peer support for discharge from acute psychiatric inpatient care using data from participants allocated to the intervention arm. Two outcomes were considered: 1) a measure of 'engaged with peer worker'; 2) number of face-to-face contacts with peer worker post-discharge. Statistical analyses used logistic and zero-inflated negative binomial regression models according to outcome structure.

Results: Data were analysed for 265 participants randomised to peer support with a known peer worker. Sixty-two percent of participants received peer support as defined as having had at least two peer worker meetings, at least one of which was in the community following discharge. The mean number of face-to-face contacts was 6.2, ranging from 0 to 22 contacts. Duration of first contact with peer worker (OR=1.03, 95% CI: 1.00, 1.04) and more relationship building activities in the first contact (OR=1.4, 95% CI: 1.13, 1.85) were associated with greater odds of engaging with peer support. For those participants with at least one contact, less days between recruitment and discharge was associated with a greater number of face-to-face contacts post-discharge, IRR=0.99 (95% BPCI: 0.99, 1.00).

Conclusions: Implementation of peer support should include a focus on taking time in the first session of peer support to build the relationship between peer and peer worker. When there are delays in discharge engagement is more challenging post discharge. No association was found between incidental matching of peers and peer workers suggesting that peer support may work 'across difference'.

**102. Miss Ella Whittle**

Protein Kinase A Regulatory Subunit IIB (PRKAR2B): A novel player in neurodevelopmental disease.

*Authors: Ella Whittle, Hannah Gulliford, Ehsan Ghayoor, Debby Hellebrekers, Melanie O'Leary, Lynn Pais, Reza Maroofian, Erika Ignatius, Yalda Jamshidi, Alan M. Pittman, Henry Houlden, Christopher J. Carroll*

Introduction: Protein Kinase A (PKA) is a well-known cell signalling complex essential to cellular proliferation, homeostasis and growth. PKA consists of two catalytic subunits under the control of a regulatory subunit dimer encoded by the gene protein kinase cAMP-dependent type II regulatory subunit type II beta (PRKAR2B).

PKA is known to have a role in neurodegenerative disease, however, the regulatory subunit, PRKAR2B, has not yet been linked to disease. Here, we report four unrelated families with neurodevelopmental disease harbouring pathogenic variants in PRKAR2B, establishing PRKAR2B as a cause of rare neurodevelopmental disease.

Methods and Results: We present three novel PRKAR2B variants in four unrelated families identified using whole-exome sequencing: two homozygous stop-gain variants, p.(Arg343Ter) and p.(Arg108Ter), and one compound heterozygous variant, p.(Arg108Ter)/p.(Leu154Pro). Variants were prioritised due to being rare (absent or MAF <0.001 in gnomAD) and for having high CADD Phred scores (>20) indicating a likely deleterious impact. Patients presented with neurodevelopmental disease characterised by hypotony, brain atrophy, spasticity, seizure, delayed speech and language development and autistic behaviour. Thus far, evidence of pathogenicity of variants has been supported by in-silico pathogenicity predictors and measurement of endogenous PRKAR2B protein from patient cells revealing a loss of PRKAR2B protein expression in the two families that fibroblasts were available for.

Conclusion: We have identified PRKAR2B as a cause of rare monogenic neurodevelopmental disease. Our future work will try to elucidate disease mechanism and further understand the role of PRKAR2B.

**103. Mr Jacob Wildfire**

Discovering genetic barriers to the spread of AMR

*Wildfire, J., Gupta, A., Sharpe, A., Knight, G., Lindsay, J.*

The spread of antimicrobial resistance through bacterial populations is facilitated through the mechanism of horizontal gene transfer (HGT). Bacteriophage drive the HGT of antimicrobial resistance genes (ARG) into the major human pathogen Staphylococcus aureus via generalised transduction. Despite ARGs for every major class of antibiotics being observed in the S. aureus population, a completely resistant S. aureus strain has yet to be detected implying unknown barriers to HGT. This project therefore sought to identify and characterise S. aureus genes with undiscovered transfer control functions using a novel screening methodology. Through this, we have discovered 79 genes which meet this criterion, with substantial clustering patterns. We therefore propose that there are genomic islands within the S. aureus genome in which HGT barrier genes are accumulated. In addition, we have begun to characterise a sample of these genes including scpB, a condensin gene involved in DNA separation. Condensin homologs have been demonstrated to control the evolution of several other serious pathogens including Vibrio cholerae; it is possible that they may be affecting the evolution of antimicrobial resistance in S. aureus in a similar manner. This work may be the first step in uncovering new biotechnologies and gene targets for combatting the spread of resistance.

**104. Miss Kathryn Willis**

Exploring perceptions and concerns among people living with diabetes and health care professionals, about the potential deployment of Artificial Intelligence (AI) systems in the NHS Diabetic Eye Screening Programme (DESP)

*Chandrasekaran, L., Chaudhry, U., Owens, C., Rudnicka, R., Willis, K*

The English NHS Diabetic Eye Screening Programme (DESP) performs around 2.2 million eye screening appointments each year, generating over 10 million retinal images that are graded for the presence or severity of diabetic retinopathy. Currently, human graders perform this task within the DESP; however, this is expensive and time-consuming, and so human graders expertise could be applied elsewhere in the process.

We have shown that Artificial Intelligence (AI) systems can identify images with no disease from those with retinopathy as well as human graders, and could help significantly reduce the workload for human graders.

There is a need to examine the expectations/concerns of AI-assisted eye-screening among people living with diabetes (PLD) and NHS staff, if AI were to be introduced into the DESP. Staff working at the North East London NHS DESP and local PLD were invited to participate in focus groups to co-design two online surveys to understand their perceptions, concerns and views. The two surveys are comparable in content, however the survey for staff additionally examines issues relating to workforce planning. Differences in surveys responses by population subgroups including age and ethnicity will be examined.

The survey will be distributed by NHS DESP sites to staff, PLD, via patient groups on social media and charities. Using a range of recruitment routes, we hope to achieve representation from a diverse group of people. Surveys will be anonymous and analysed to show general patterns in views/attitudes of staff and PLD towards AI-assisted screening within the DESP. There will be the possibility for participants to share their contact details if they are interested in participating in further research.

These questionnaires will identify factors that may influence acceptance of this technology by staff and PLD to assist training and ease the implementation process.

**105. Miss Natasha Wollen**

Investigation of Apoptosis Regulation by ZNF516 in Pancreatic Cancer Cells.

*Wollen, N.*

Pancreatic ductal adenocarcinoma is an aggressive form of cancer with a low survival rate, attributed to the resistance it forms against current first-line treatment: gemcitabine (1). Gemcitabine is a nucleoside analogue drug which targets cancer cells by inhibiting an enzyme involved in DNA synthesis (ribonucleotide reductase), and therefore reduces cancer cell division (2). This research intends to address the ineffectiveness of gemcitabine by investigating the mechanisms behind the resistance of pancreatic cancer cells to gemcitabine. This was inspired by research suggesting that using TRAIL in combination with gemcitabine could optimise its pro-apoptotic function and lead to effective pancreatic cancer cell destruction, due to an association with increased 4E-BP1 expression in a hypophosphorylated state (3). Gene ZNF516 was identified during a search of genome-wide CRISPR-Cas9 data which aimed to find genes linked to TRAIL-signalling and apoptosis implicated in pancreatic cancer (Elia and Miralles, unpublished). The research presented by this poster focuses on the investigation of the role of gene ZNF516 in regulation of genes involved in the TRAIL signalling pathway, in the aim of advising effective alterations to currently available treatment strategies for pancreatic cancer.

**106. Mrs Helen Wood**

Work and social adjustment scale used as a tool in Subarachnoid and Arteriovenous Malformation patients to assess improvement and adjustment overtime.

*Helen Wood*

Background: Patients have on-going needs following a Subarachnoid Haemorrhage (SAH) and Arteriovenous Malformation (AVM) bleed (Wood et al 2020). The Neurovascular CNSs in two separate telephone clinics utilised the Work and social adjustment scale (WSAS) to assess need (Mundt, Marks et al 2018). By using the WSAS we could have a clearer indicator when more support was needed.

Aims: To assess improvement and adjustment over two separate telephone clinics. Utilise the WSAS as an indicator to assess further support requirements for patients following SAH and AVM at CNS telephone clinic.

Demographics: 33 patients / 21F 12M 7:3 ratio Age range 28-81 years. Median age 54 years.

Methods: At the end of the telephone clinic the patient was asked if they would participate in the WSAS to score their lived experience. This was repeated in the second clinic.

Results:

- 8 patients scored greater than 20 on their first clinic WSAS
- 6 patients scored greater than 20 on their second clinic WSAS
- Only 1 patient scored over 20 in the second clinic and less than 20 in the first clinic
- Higher score of work impact in the second clinic may be due to having re-started work and then realising the impact
- Home, personal, and social impact, scored nearly equally in both clinics
- The impact on the family less evident in the scores in both clinics although a bit higher in the first clinic.

Conclusion:In the second call personal, home and family scores had decreased the work and social scores had increased as the individuals had tried to get back to the normal lives. To conclude these patients may benefit from Neuro-physiology support.

Reference:Mundt J, Marks I, et al 2002. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. British Journal of Psychiatry. 180(5), 461-464. http://doi.org/10.1192/bjp.180.5.461

Wood, H. et al 2020 A review of telephone clinic letters for patients with subarachnoid haemorrhage and arteriovenous malformations. British Journal of neuroscience Nursing. 16(6), 72-278. https://doi.org/10.12968/bjnn.2020.16.6.272

**107. Miss Emily Woodcock**

Scanning Ion Conductance Microscopy: A novel method for investigating melanoma cell stiffness

*Woodcock, E., Valderrama, F., Korchev, Y., Sviderskaya, E.*

Scanning ion conductance microscopy (SICM) is a technique which allows non-invasive examination of live cell topography and structure under physiological conditions. SICM has recently been adapted to measure cell stiffness. Metastasis plays a vital role in cancer progression and is correlated with changes in the cytoskeletal network and cell stiffness. It has previously been shown that softer cells show higher metastatic and migratory abilities. However, other publications have shown opposing results, as is the case for melanoma. Furthermore, changes in cell stiffness can also provide information about drug treatment and its effectiveness. Here, we aim to be the first to assess the correlation between cell stiffness and metastatic potential of melanoma cell lines using SICM and to evaluate changes in cell stiffness following the treatment of anti-cancer drugs.

An examination of the stiffness of melanoma cell lines with varying metastatic potential was carried out using SICM. We also used the continuous scanning method to assess cell stiffness changes in melanoma cells following treatment with anti-cancer drugs such as Taxol and Cisplatin.

We saw an increase in the mean stiffness in the highly metastatic cell line. This goes against the consensus that metastatic cells are softer to allow increased motility. It is hypothesised this may be due to increased metastatic cell plasticity. Our data highlights the variability between studies and cancer types when using cell stiffness as a biomarker for metastatic potential. Treatment of melanoma cells with Taxol and Cisplatin saw an overall increase in cell stiffness following treatment. This suggests that cell stiffness may be an overlooked effect of some anti-cancer drugs. However, the work showed variability in the change of cell stiffness between cells, highlighting heterogeneity in the effect of anti-cancer drug treatment.

**108. Jane Watson**

Prevalence of anxiety and depression in patients with severe Asthma who are receiving biologic therapy.

*J.S. Watson, C. Peach, N. Price, J. Evans, A. Draper, S. Ruickbie*

There is limited evidence currently on the mental well-being of patients with severe Asthma, although those with severe Asthma and steroid dependency have been shown to have statistically

significant increases in both anxiety and depression scores (2). Psychological support for this patient population is internationally recommended.

Aim: To understand the prevalence of anxiety and depression in patients with severe Asthma, receiving biological therapy and to identify effects on Asthma control.

Methods: Patients (n49) with severe Asthma and who were receiving Asthma biologic therapy, were invited at a respiratory out-patient review to complete three quality of life questionnaires (HADS, ACQ6 and ACT) at two time points, eight months apart.

Results: There was an association between the variables ACQ6 and HADS (p=0.038; p=0.031) and ACT and HADS (p=0.035; p=0.039) at both start and end points. Patients on antidepressants had higher HAD scores than those not, which was statistically significant (p=0.034). No male patients were taking antidepressants

Conclusion: This cohort of patients with severe Asthma had high levels of anxiety and depression which worsened asthma symptoms and overall disease burden. Measuring and treating anxiety and depression, including support from psychological therapies is recommended.

**109. Jane Watson**

A respiratory ward oxygen audit to ascertain in-patient oxygen administration and self-reported knowledge and actions of ward staff.

*Watson JS, Price, N. Matimba, Y. Peach C, Griffin D, Blackmore L*

Background: Oxygen therapy is a drug which needs prescribing and monitoring. Over and under oxygenation has significant effects upon patient outcomes (1). The trust utilises the BTS emergency oxygen guidelines (1), alongside National Early Warning Score (NEWS)2 charts to monitor and manage appropriate target saturations for individual patients.

Aim: To understand current oxygen therapy on an acute respiratory ward and to investigate health care practitioners reported oxygen knowledge and actions.

Methods: n22 episodes of patient oxygen utilisation across an acute respiratory unit were anonymously reviewed against physical patient assessment and their electronic health records, including prescription charts. Simultaneously, ward staff (n26) were surveyed to ascertain oxygen knowledge base and reported actions.

Results: Approximately two thirds (14/22) of patients receiving oxygen had no prescription and 5/22 (23%) had no clearly documented oxygen target range. Of those with specified target saturations (n17), 53% were using oxygen within specified range; of which 35.3% (6/17) were above (range 1-8%, mean 3.5%) and 12% 2/17 below target.

Conclusion: Most patients receiving oxygen therapy had no prescription. Target saturations are more often specified on the NEWS2 chart rather than the prescription chart, yet this can be specified by a range of staff including those unqualified. Oxygen appeared to be frequently prescribed when there was an 88-92% target, however the prescription is only on the PRN side. Despite 80% of qualified staff stating they would always check the prescription chart for patients receiving oxygen, there were no recordings that oxygen had been administered on any of the prescription charts. Interventions to address these shortcomings are in progress.

**110. Jane Watson**

Informing an intervention to improve referral to Pulmonary Rehabilitation (PR) for patients with Chronic Obstructive Pulmonary Disease (COPD): A survey of primary health care practitioners.

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Postgraduate (including MRes and MD) prize (£100) Background: PR is an important treatment for patients with COPD, yet referral rates are persistently low and effective interventions to improve referral rates limited.

Aim: To identify the most promising interventions to enhance PR referral-in primary care Methodology: Primary healthcare practitioners working in United Kingdom GP settings.

Results: There were 222 respondents (n=88 online) including 129 nurses, 57 advanced nurse practitioners, 29 general practitioners and 7 allied health professionals. The top five rated and ranked interventions are shown in table 1.

Table 1 Section b: Likert exercise (n203-207)

PR providers engaging with practice staff * 171/203 (90.2%)

HCP referring patients at time of COPD diagnosis. 70/138 (50.7%)

Greater awareness of PR in practice. i.e Posters, 170/204 (86.3%) Educational sessions for GP staff. * 60/138 (43.5%) Educational sessions for GP staff * 174/204 (86.3%)

Section c: Ranking Exercise (ordered 1-5) (n127-138)

PR providers directly contacting eligible patients.* 52/127 (41%)

Educational for patients, carers and family.* 174/206 (84.5%) Educational sessions for potential patients, carers and family.* 47/138 (34%)

Patients self- referral 173/205 (84.4%)

A standardised summary that describes PR 46/138 (33.3%)

Conclusion: PHCPs suggested a range of potential PR referral interventions that relate to time of referral, PR education and awareness and direct referral opportunities. Suggestions span patients, practice staff and/or PR providers. In the absence of evidence-based interventions, testing these suggestions are likely to be advantageous next steps."

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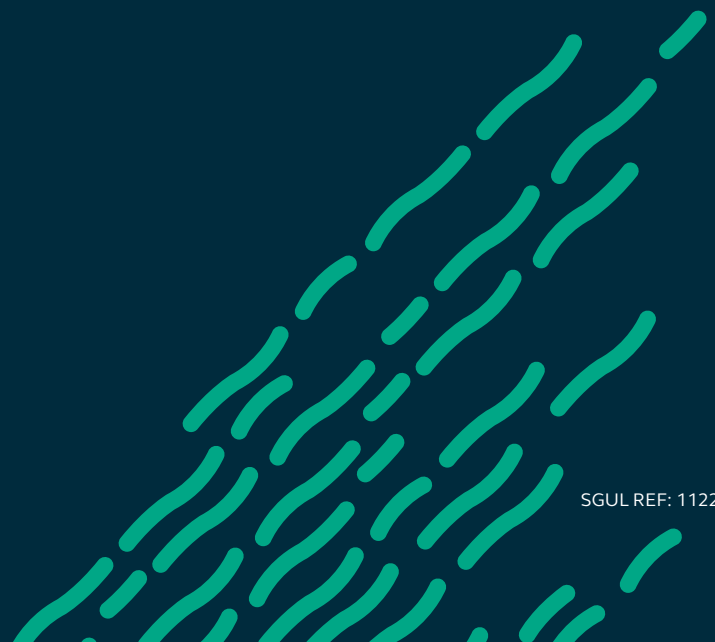

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