Imperial College London

NATIONAL HEART AND LUNG INSTITUTE RESEARCH AWAY DAY

MONDAY 25 SEPTEMBER 2023

WE ARE EXTREMELY GRATEFUL TO THE SPONSORS FOR THIS EVENT

AstraZeneca GSK SIEMENS Healthineers

Follow NHLI on Twitter @ImperialNHLI – use #NHLIAwayDay to join the conversation

Vote for the presentations by visiting: https://www.menti.com/alo3aobn9jtf

REGISTRATION from 08:15	**QEII CONFERENCE CENTRE WESTMINSTER SW1P 3EE**
08:15	**COFFEE IN CAMBRIDGE SUITE 5th FLOOR**
09:05	**MOUNTBATTEN SUITE 6TH FLOOR**
09:05-09:10	**Clare Lloyd** *Welcome and Opening Remarks*
TOPIC 1	**BIG DATA, ARTIFICIAL INTELLIGENCE AND -OMICS**
09:10-9:30 Flash Presentations	**01 Abdul Qayyum** *Cardiac Function* Unsupervised Domain Adaptation Attention-Guided Generative Adversarial and Efficient 3D volumetric Probabilistic Diffusion Deep learning models for Four-Chamber Whole Heart Segmentation and Reconstruction
	02 Alex Cucco *Inflammation, Repair and Development* On the Use of Graph and Manifold Theory for Multi-source Data Integration in Medical Research
	03 Justie Mak *Genomic and Environmental Medicine* The Adverse Health Effects of Occupational Exposure to PM2.5 on the London Underground
	04 Benedict Reilly-O'Donnell *Cardiac Function* Novel platform for the multiplexed detection of blood serum biomarkers
	05 Kavitha Vimalesvaran *Cardiovascular Trials and Epidemiology* The ratio of SSFP blood signal ratio between the ascending aorta and left ventricle predicts aortic stenosis severity: a retrospective analysis

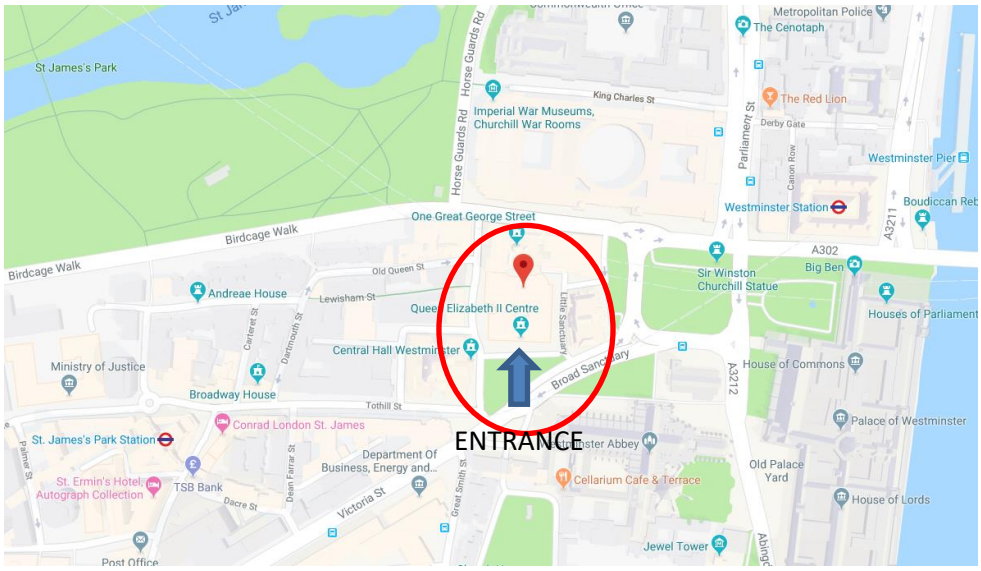
09:30-09:45	**Kathryn McGurk** *Genetics and Imaging* Adult cardiac trabecular morphology: a biomarker of cardiomyopathies
09:45-10:00	**Hernan Fainberg** *Inflammation, Repair and Development* Classification of patients with Idiopathic Pulmonary Fibrosis according to blood biomarker signatures by consensus cluster analysis: a multiple machine learning approach
10:00-10:15	**Arunashis Sau** *Cardiac Function* Exploring the prognostic significance and important phenotypic and genotypic associations of neural network-derived electrocardiographic features
TOPIC 2	**TRANSLATING RESEARCH TO CLINICAL PRACTICE**
10:15-10:30 Flash Presentations	**06 Sean Zheng** *Genetics and Imaging* Large-scale genome-wide association study in over one million participants highlight insights in genetic architecture and cellular biology in dilated cardiomyopathy
	07 Benjamin Fletcher *Cardio-Respiratory Interface* Investigating the Roles of miR-424 and miR-542 in Muscle Atrophy
	08 Parris Williams *Airways Disease* Immediate smoking cessation support during lung cancer screening: long term outcomes from two randomised controlled trials
	09 Fama Manneh *Vascular Science* Development of an enhanced charged novel superhydrophobic haemostatic device
10:30	**COFFEE AND POSTERS IN CAMBRIDGE SUITE 5th FLOOR**
11:15	**MOUNTBATTEN SUITE 6TH FLOOR**
11:15-11:30	**Simone Hadjisymeou Andreou** *Respiratory Infections* Is sputum Galactomannan a feasible screening test for Aspergillus infection in Paediatric Cystic Fibrosis patients?
11:30-11:45	**Niamh Errington** *Vascular Science* Diagnostic miRNA signatures for treatable forms of pulmonary hypertension highlight challenges with clinical classification
11:45-12:00	**Jakob Jonnerby** *Genomic and Environmental Medicine* Viral RNA decline time predicts transmission of SARS-CoV-2 and Influenza
12:00-12:15	**Dario (Roberto) Sesia** *Cardiovascular Trials and Epidemiology* Predicting All-Cause Mortality and Acute Coronary Syndrome Risk Using Machine Learning
TOPIC 3	**EXPERIMENTAL MODELS OF DISEASE**
12:15-12:30	**Jenny Katsouli** *Airways Disease* Alveoli-on-a-chip integrated onto a fluorescence microscope to direct observe pathophysiological mechanisms

12:30-12:45	**Dana E. Al-Ansari** *Vascular Science* Biomaterial-Driven 3D in vitro Spheroid-Based Lymphangiogenesis Model Using Click Crosslinked Hydrogels
12:45-13:00	**Ciara Campbell** *Inflammation, Repair and Development* Altered airway epithelial cell function in children with severe asthma following co-exposure with repeated HDM and Respiratory Syncytial Virus
13:00	**LUNCH BREAK AND POSTER SESSIONS** **WINDSOR SUITE**
14:10	**MOUNTBATTEN SUITE** **6TH FLOOR**
14:10-14:30 Flash Presentations	**10 Zuzanna Jablonska** *Cardiac Function* The secretome of cardiac mesenchymal stromal cells protects human cardiomyocytes from in vitro ischaemia-reperfusion injury
	11 Anthony Sinadinos *Respiratory Infections* F/HN-pseudotyped lentiviral vector-mediated transduction of non-human primates
	12 Maike Haensel *Vascular Science* Microfluidic platform for modelling of alveolar-vascular cell interactions in pulmonary hypertension (PH) associated with chronic obstructive pulmonary disease (COPD)
	13 Alexia Martin *Airways Disease* 4D live imaging for anti-mitotic chemotherapy predictive biomarker identification in 3D patient-derived organoid tumour models
	14 Andreia Sofia Bernardo *Cardiac Function* Generation of left ventricle-like cardiomyocytes with improved structural, functional, and metabolic
TOPIC 4	**MECHANISMS UNDERLYING HEALTH AND DISEASE**
14:30-14:45	**Mascha Vinokurova** *Cardio-respiratory Interface* Targeting the Rgl1 pathway to control vascular inflammation and atherogenesis
14:45-15:00	**Amber Owen** *Respiratory Infections* Presence of neutrophils in the lungs prior to infection with RSV alters disease severity in mice
15:00-15:15	**Michael Lee** *Cardiac Function* A cell and gene atlas of chronic ischaemic heart failure
15:15-15:35 Flash Presentations	**15 Claudia Efstathiou** *Respiratory Infections* Long Covid symptoms are driven by distinct proteomic profiles
	16 Qi Chen *Cardio-respiratory Interface* Investigating injury- and ageing-related alterations in lung tissue-derived extracellular vesicles and their effects on lung tissue

	17 Seran Hakki *Genomic and Environmental Medicine* Early rapid zinc metabolism has a role in determining optimal outcome post SARS-CoV-2 infection
	18 Eleni Vasilaki *Vascular Science* Use of multi-omics to uncover novel and druggable targets of SOX17 in PAH
	19 Joy Nakawesi *Respiratory Infections* The role of type I interferons in the generation of tissue-resident memory CD8+ T cell responses during RSV infection
	KEYNOTE SPEAKER
15:35-15:55	**Steven Niederer** Cardiovascular Digital Twins
15:55-16:00	**Clare Lloyd** *Awards and Prizes*
16:00-17:00	**DRINKS RECEPTION** **CAMBRIDGE SUITE**

QUEEN ELIZABETH II CONFERENCE CENTRE

QEII Conference Centre, Broad Sanctuary, Westminster, SW1P 3EE



NEAREST TUBE STATION

St James's Park: 4 mins walk
Westminster: 6 mins walk
Victoria: 14 mins walk

NEAREST MAINLINE STATIONS

Charing Cross: 12 mins walk
Victoria: 14 mins walk
Waterloo: 18 mins walk

WE ARE VERY GRATEFUL TO OUR SPONSORS WHO WILL BE ATTENDING

AstraZeneca	Catherine Overed-Sayer Tina Baker	Director, Bioscience COPD and IPF catherine.overed-sayer@astrazeneca.com Principal Scientist, Translation Science and Experimental Medicine tina.baker@astrazeneca.com
GSK	James Bolaji Ben Egan	Medical Scientist Liaison (Severe Asthma) james.x.bolaji@gsk.com Medical Science Liaison (Specialty Medicine) ben.x.egan@gsk.com
SIEMENS Healthineers	Craig Buckley Scott Sinclair	Head of Research and Scientific Collaborations craig.buckley@siemens-healthineers.com Business Manager Digital Health scott.sinclair@siemens-healthineers.com

PLEASE BE SURE TO VISIT THE EXHIBITORS ON THE 5TH FLOOR

APPLETON WOODS LTD	Sam Garvey Matthew Harris	Sam.Garvey@appletonwoods.co.uk 07881 952291 mharris@andprecision.com 0121 4587740
avantor™	Emma Waterfield Sam Ahmed	emma.waterfield@avantorsciences.com 0755 7172975 sam.ahmed@avantorsciences.com 07557 822702
Haier Biomedical Intelligent Protection of Life Science	Harry Pomfret	harry.pomfret@haierbiomedical.co.uk 07757 875 986
MERCK	Elham Shirazi Aimee Parson	elham.shirazi@merckgroup.com 07721 628706 aimee.parsons@merckgroup.com
NEW ENGLAND BioLabs	Anne-Marie Mooney	amooney@neb.com 07557 475108
SARSTEDT	Matthew Yates Shereen De Silva	matthew.yates@sarstedt.com 07970220126 shereen.desilva@sarstedt.com 07970220127
Thermo Fisher SCIENTIFIC	Adam Zayer Karina Caetano Souza	adam.zayer@thermofisher.com 07768 776797 karina.caetanosouza@thermofisher.com 07824 081075

ABSTRACTS

TOPIC 1	BIG DATA, ARTIFICIAL INTELLIGENCE AND -OMICS

ORAL PRESENTATIONS

Kathryn McGurk
k.mcgurk@imperial.ac.uk

Adult cardiac trabecular morphology: a biomarker of cardiomyopathies

Kathryn A McGurk[1], Pawel Tokarczuk[2], Wenjia Bai[3], Mengyun Qiao[3], Sean L Zheng[1], James S Ware[1,2,4] and Declan P O'Regan[2]
[1] National Heart and Lung Institute; [2] MRC London Institute of Medical Sciences; [3] Department of Computing, Imperial College London; [4] Royal Brompton & Harefield Hospitals, Guy's and St. Thomas' NHS Foundation Trust

Cardiac trabeculae form a network of muscular strands that line the inner surfaces of the heart. It remains unclear whether the observed variation in adult trabeculation has a role in cardiovascular disease and remodelling. We analysed cardiac MRI-derived phenotypes measuring trabecular morphology (TM) in the left ventricle of 50,000 adults of the UK Biobank to assess whether hypertrabeculation is a biomarker of CVD and to understand the relationship between the variation in adult TM and clinical outcomes.

Physical activity and African ancestry significantly increased TM ($P<0.05$), with CMR measures of volume (LVEDV ($R=0.24$), LVESV ($R=0.22$)) and strain (Err ($R=-0.15$), Ecc ($R=0.23$)) having the strongest relationship with TM. Participants diagnosed with cardiomyopathies, heart failure, fibrillation and flutter, conduction disorders, and valve diseases, among others, were significantly associated with increased TM ($P<0.05$).

We identified for the first time, rare variants with influences over variation in TM. The genes identified include those involved in inherited cardiac conditions (CASQ2, MYBPC3, TTN, CRYAB), calcium and potassium channels (CACNA1C, KCNJ14, KCTD4), heparin sulfate (EXTL1), muscle development (CSRP3, LRIF1), and neurodevelopment (CEP85L, COG5, GRIA1). We identified novel genes from GWAS (e.g., FHL2, STRN, FLNB, NKX2-5, NOTCH1).

Subclinical carriers of CM-associated pathogenic variants had increased TM, for phenotypically opposed HCM and DCM, providing evidence that trabeculation may be a useful biomarker of the evolution of cardiomyopathic remodelling and abnormal loading conditions. Ongoing work: we are undertaking analyses of the right ventricle to allow for assessments of pulmonary hypertension and arrhythmogenic cardiomyopathy, and sequencing patients previously diagnosed with LVNC.

Hernan Fainberg
h.fainberg@imperial.ac.uk

Classification of patients with Idiopathic Pulmonary Fibrosis according to blood biomarker signatures by consensus cluster analysis: a multiple machine learning approach

HP. Fainberg[1], JMB. Sand[2], JM. Oldham[3], PL. Molyneaux[1,4], WA. Fahy[5], J. Porte[6], R. Braybrooke[6], G. Saini[6], MA. Karsdal[2], DJ. Leeming[2], I. Triguero[8], E. Oballa[2], A. Wells[1,4], E. Renzoni[1,4], LV. Wain[9,10], I. Noth[11], TM. Maher[1,4,12], ID. Stewart[1] and RG. Jenkins[1,4]
[1] National Heart and Lung Institute; [2] Nordic Bioscience, Herlev, Denmark; [3] Division of Pulmonary, Critical Care & Sleep Medicine, University of California; [4] Royal Brompton & Harefield Hospitals, Guy's and St. Thomas' NHS Foundation Trust; [5] Discovery Medicine, GlaxoSmithKline; [6] Nottingham Respiratory Research Unit, University of Nottingham; [7] Computational Optimisation and Learning Lab, School of Computer Science, University of Nottingham; [8] Department of Health Sciences, University of Leicester; [9] Leicester Respiratory Biomedical Research Centre, Glenfield Hospital; [10] Pulmonary and Critical Care Medicine, University of Virginia; [11] Keck School of Medicine, University of Southern California

Background: Idiopathic pulmonary fibrosis (IPF) is a fatal disease characterised by remodelling of the pulmonary extracellular matrix (ECM), leading to disrupted lung function. Endotyping IPF through ECM components could improve patient management. While Forced Vital Capacity (FVC) decline indicates prognosis and progression, IPF endotypes remain unclear.

Methods: We analysed data from the PROFILE study, a prospective cohort of IPF patients, collecting serum samples at baseline to measure a panel of 13 blood biomarkers of degraded ECM proteins by ELISA-based neoepitope assay. We performed unsupervised consensus clustering, machine learning, transfer machine learning, statistical and sensitivity evaluation tools, comparing clusters by anthropometric features and clinical outcomes. We replicated analysis on the Australian Idiopathic Pulmonary Fibrosis Registry cohort using transfer learning.

Results: 462 (~80%) of 580 participants were eligible for analysis. We identified three IPF clusters: CL1-3, associated with distinct 5-year outcomes (log-rank p=0.0001). CL2 was the worst clinical outcomes, with 79 (72.48%) of 109 patients dying 5 years post-diagnosis. CL1 was characterised by an increase in clotting resolution factor XFIB, while CL2 had lower PROC4 and PROC28 biomarkers than CL3, and CL2 had higher MMP7, SPD, CYFRA211, CA199 and CA125. Baseline ppFVC was significantly higher in CL3 and CL1. The replication cohort showed similar biomarker ratios and lung function.

Conclusions: We identified blood biomarkers capable of distinguishing IPF patient groups with significant survival differences and clinical characteristics. These findings support multiple endotypes of IPF, aiding patient management and therapy development. Machine learning tools could aid IPF patient stratification and outcome prediction.

Arunashis Sau
arunashis.sau09@imperial.ac.uk

Exploring the prognostic significance and important phenotypic and genotypic associations of neural network-derived electrocardiographic features

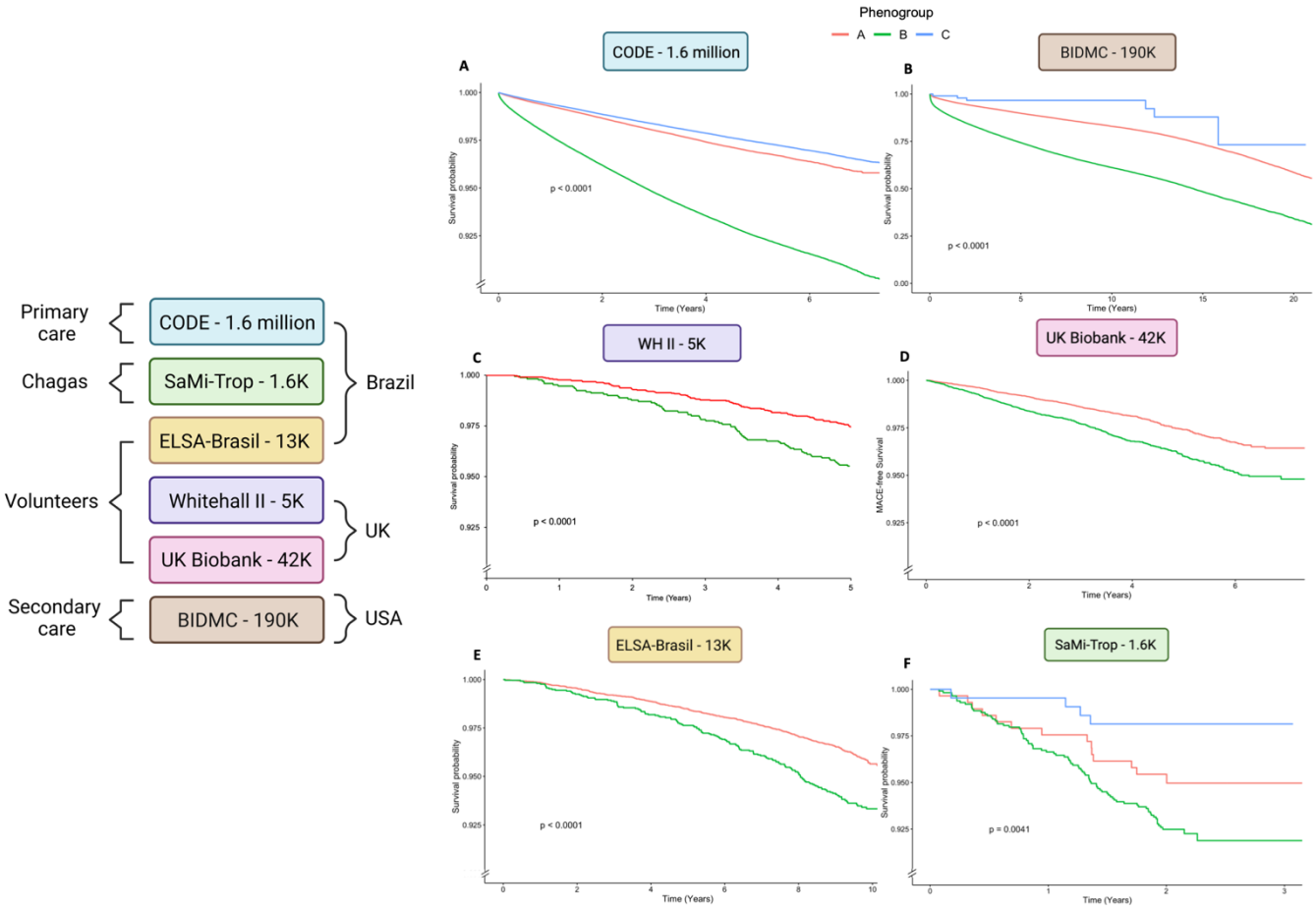
Arunashis Sau[1,2], Antônio H. Ribeiro[3], Kathryn A. McGurk[1,11], Libor Pastika[1], Nikesh Bajaj[1], Maddalena Ardissino[1], Jun Yu Chen[1], Huiyi Wu[1], Xili Shi[1], Katerina Hnatkova[1], Sean Zheng[1], Annie Britton[4], Martin Shipley[4], Irena Andršová[5], Tomáš Novotný[5], Ester Sabino[6], Luana Giatti[7], Sandhi M Barreto[7], Jonathan W. Waks[8], Daniel B. Kramer[1,9], Danilo Mandic[10], Nicholas S. Peters[1,2], Declan P. O'Regan[11], Marek Malik[1,5], James S. Ware[1,11,12], Antonio Luiz P. Ribeiro[13] and Fu Siong Ng[1,2]

[1] National Heart and Lung Institute; [2] Department of Cardiology, Imperial College Healthcare NHS Trust; [3] Department of Information Technology, Uppsala University; [4] Research Department of Epidemiology and Public Health, University College London; [5] Department of Internal Medicine and Cardiology, University Hospital Brno and Masaryk University, Czech Republic, [6] Department of Infectious Diseases, University of São Paulo, Brazil; [7] Department of Preventive Medicine and Hospital das Clínicas/EBSERH, Universidade Federal de Minas Gerais; [8] Harvard-Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, USA; [9] Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, USA; [10] Department of Electrical and Electronic Engineering, Imperial College London; [11] MRC London Institute of Medical Sciences; [12] Royal Brompton & Harefield Hospitals, Guy's and St. Thomas' NHS Foundation Trust; [13] Department of Internal Medicine, Hospital das Clínicas, Universidade Federal de Minas Gerais, Brazil

Background: Subtle, prognostically-meaningful ECG features may not be apparent to physicians. In the course of supervised machine learning training, many thousands of ECG features are identified. These are not limited to conventional ECG parameters and morphology. These novel neural network (NN)-derived ECG features may have clinical, phenotypic, and genotypic associations and prognostic significance.

Methods and Results: We extracted 5120 NN-derived ECG features from an AI-ECG model trained for six simple diagnoses and applied unsupervised machine learning to identify three phenogroups. The derivation set (CODE cohort, n = 1,558,421), is a database of ECGs recorded in primary care in Brazil. The three phenogroups had significantly different mortality profiles (Figure 1A). We externally validated our findings in five diverse cohorts (Figure 1B-F), phenogroup C was not well represented in some cohorts. We found phenogroup B had a significantly greater risk of mortality in all cohorts (Figure 1). Using a phenome-wide association study (PheWAS) we found ECG phenogroup significantly associated with cardiac and non-cardiac phenotypes, including cardiac chamber volumes and cardiac output. A genome-wide association study yielded significant loci in SCN10A, SCN5A and CAV1 and ARHGAP24. Mendelian randomisation demonstrated the higher risk ECG phenogroup was causally associated with higher odds of atrioventricular block but lower odds of atrial fibrillation and ischaemic heart disease.

Conclusion: NN-derived ECG features have important clinical and biological significance beyond the original model from which they are derived and may be transferable and applicable for risk prediction in a wide range of settings, in addition to mortality prediction.



FLASH PRESENTATIONS

01 Abdul Qayyum
a.qayyum@imperial.ac.uk

Unsupervised Domain Adaptation Attention-Guided Generative Adversarial and Efficient 3D volumetric Probabilistic Diffusion Deep learning models for Four-Chamber Whole Heart Segmentation and Reconstruction

Abdul Qayyum[1], Cristobal Rodero[1] and Steven Niederer[1,2]
[1] National Heart and Lung Institute; [2]The Alan Turing Institute

To address the lack of large amounts of labelled medical data, domain adaptation (DA) has been of strong interest in the medical imaging community. DA is a subcategory of transfer learning that aims at bridging the domain distribution discrepancy between the source domain and the target domain. Due to lack of manual annotated dataset in one modality, we need to transform the style of source modality to target modality.
In this abstract, we have proposed Attention-guided Generative adversarial and efficient 3D volumetric probabilistic diffusion deep learning models for 4CH whole heart segmentation and reconstruction using private non-annotated clinical MRI and open source annotated MICCAI challenge datasets. The open source MICCAI challenges dataset has abandoned annotation while our private clinical MRI dataset has no manual annotation. We first generated the target clinical MRI data from unpaired MICCAI challenges datasets using Attention-guided Generative adversarial network and transform the style or miss alignment pixels from unpaired source MICCAI annotated datasets to our private non-annotated dataset and then segment left ventricle (LV), right ventricle (RV), left arterial (RA), and right atrial (RA) using 3D volumetric probabilistic diffusion model. Further A 3D UNet was trained and tested using 2CH and 4CH segmentations generated from 3D coronary computed tomography angiography (CCTA) segmentations. The sparse input label map volume was converted to a dense label map by the label completion network, giving dense volumetric label maps of the LA, LV, left/right pulmonary veins. Our proposed model achieved better performance using the generated clinical MRI without annotated labels.

02 Alex Cucco
a.cucco20@imperial.ac.uk

On the Use of Graph and Manifold Theory for Multi-source Data Integration in Medical Research

Alex Cucco[1], Nazanin Zounemat-Kermani[2], Angela Simpson[3], Clare Murray[3], Ian Adcock[1], Sara Fontanella[1] and Adnan Custovic[1]
[1] National Heart and Lung Institute; [2] Data Science Institute, Imperial College London; [3] Division of Infection, University of Manchester

Introduction: The increasing availability of multi-source data, including genomic, transcriptomic, proteomic, metabolomic, and clinical, has enabled a more comprehensive understanding of complex biological systems. However, integrating these diverse datasets remains a significant challenge. Network analysis has emerged as a powerful tool for integrating different types of data from various sources, enabling the identification of common patterns and interactions. In the medical field, multi-source data integration can be applied to a range of problems, such as biomarker discovery, disease prediction and phenotype discovery.

Methods: We propose a framework for multi-source data integration using statistical modelling for network data. Graph and manifold theory were employed to construct and analyse networks, with a focus on identifying disease mechanisms. To validate the proposed framework, we applied it to multi-omics data collected in the U-BIOPRED consortium to investigate mechanisms of severe asthma and component-resolved diagnostic data obtained in the MAAS cohort to evaluate allergic sensitisations.

Results: The network-based approach effectively integrated multi-omics data to investigate disease heterogeneity. The integration of multi-omics data revealed distinctive asthma phenotypes, some preferentially associated with the severe spectrum. Similarly, the network-based approach identified key features that distinguish and characterise the evolution of allergic sensitisation over time while highlighting consistent differences between asthmatics and non-asthmatics.

Conclusions: Our study demonstrates the potential of the network-based approach for integrating multi-source data to investigate disease development. The construction of networks enables the identification of complex interactions and patterns that are difficult to detect through traditional approaches.

03 Justie Mak
j.mak21@imperial.ac.uk

The Adverse Health Effects of Occupational Exposure to PM2.5 on the London Underground

Justie Mak[1,2,3], Johanna Feary[1,4], André F. S. Amaral[1,5], Emma Marczylo[3,6], Paul Cullinan[1] and David C. Green[2,3]
[1] National Heart and Lung Institute; [2] MRC Centre for Environment and Health, Imperial College London; [3] HPRU in Environmental Exposures and Health, Imperial College London; [4] Department of Occupational and Environmental Medicine, Royal Brompton Hospital; [5] NIHR Imperial Biomedical Research Centre; [6] Toxicology Department, UK Health Security Agency

The concentrations of particulate matter (PM2.5) in the London Underground (LU) network are higher than those found above ground. However, due to physicochemical differences between PM2.5 in the LU and in outdoor air, so the health impacts associated with PM2.5 in the LU are largely unquantified. We aimed to quantify PM2.5 exposure of LU staff and assess its impact on cardiorespiratory sickness absence.

We developed a job exposure matrix to assign PM2.5 exposure to staff based on jobs. Measurement campaigns across the LU were deployed to validate staff PM2.5 exposure, which was linked to sickness absence records of 29,744 staff (2014-2019). Mixed models were used to assess associations between exposure and sickness absence.

Staff PM2.5 exposure in the LU varied by job grade. Drivers had the highest exposure (median: 130 µg/m3). Drivers had the highest rate of sickness absence (incidence rate ratio (IRR): 1.60, 95%CI 1.55-1.66), followed by fleet workers (IRR 1.39, 95%CI 1.32-1.47) and customer service staff (IRR 1.33, 95%CI 1.29-1.37), as compared to unexposed office workers. Drivers more likely to be absent due to respiratory infections (IRR: 1.12, 95%CI 1.07-1.18). Chronic respiratory and cardiovascular sickness absences were not associated with PM2.5 exposure.

Drivers who are regularly exposed to the highest concentrations of PM2.5 are the most likely to report sickness absences, compared to staff who are less exposed. This is the largest study to quantify PM2.5 exposure and the associated health effects within a London occupational cohort, which can contribute to a safer working environment for staff.

04 Benedict Reilly-O'Donnell
b.reilly-odonnell@imperial.ac.uk

Novel platform for the multiplexed detection of blood serum biomarkers

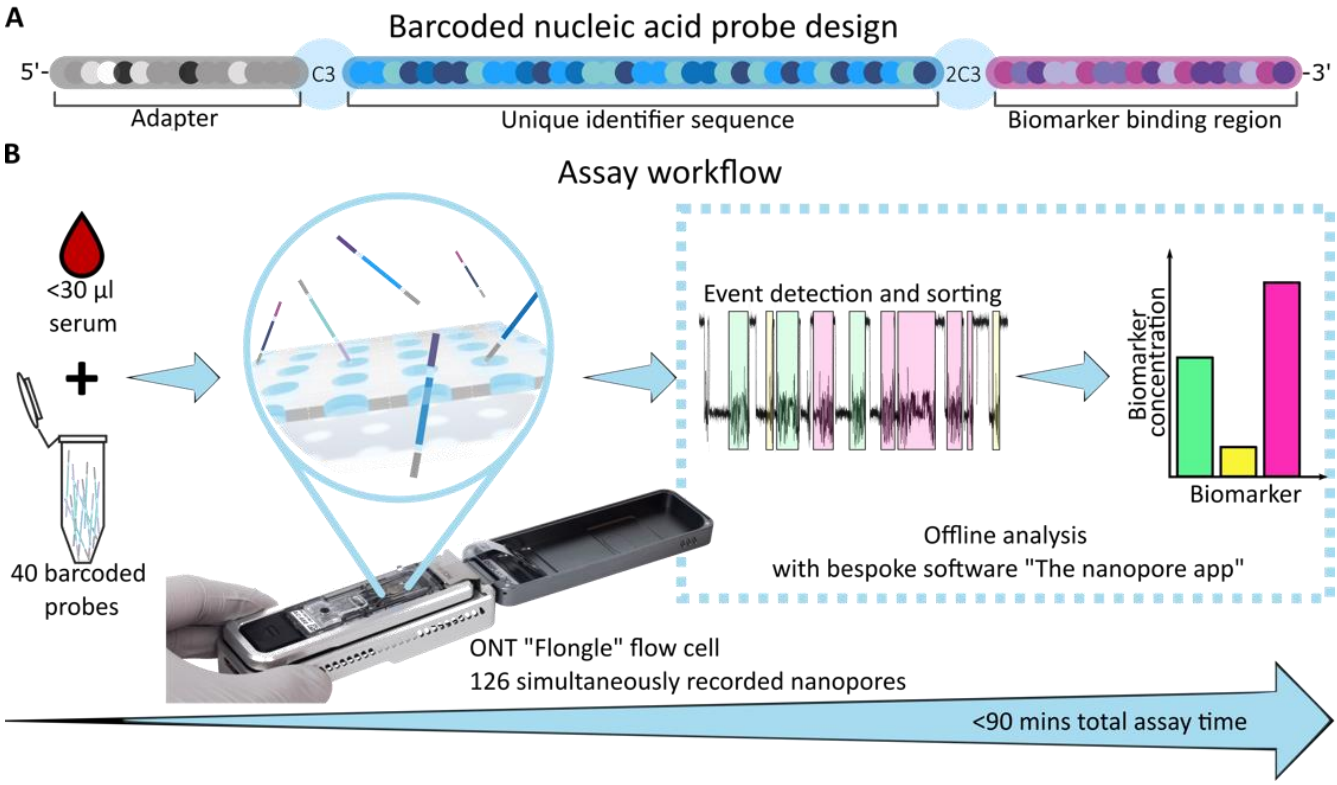
Benedict Reilly-O'Donnell[1,2], Caroline Koch[2], Richard Gutierrez[3], Carla Lucarelli[1], Fu Siong Ng[1], Julia Gorelik[1], Aleksandar P Ivanov[2] and Joshua B Edel[2]
[1] National Heart and Lung Institute; [2] Department of Chemistry, Imperial College London; [3] Oxford Nanopore Technologies, Oxford

Clinical blood tests usually rely on a single protein biomarker for determining the disease status of a patient. The use of a limited number of biomarkers often means that it is not possible to provide clinically useful information on the disease pathology. For example, elevated B- type natriuretic peptide (BNP) is an indicator of heart failure but its levels are also heightened in other cardiac conditions such as hypertension, cardiac inflammation, and myocardial infarction. Advancements in our understandings of omics mean that there is now an opportunity to expand biomarker testing beyond individual protein measurements.

In this study we aimed to produce a low-cost, rapid, quantitative, multiplexed platform for the detection of miRNAs, proteins and small molecules in blood serum.

To meet this aim, we combined a nanopore sequencing with barcoded nucleic acid probes. Each barcoded probe contains a biomarker binding region and a unique identifier sequence or "barcode" (Figure 1A). The unique identifier sequence produces a characteristic electrical current when the probe moves through a nanopore. This barcoding method, along with observation of the translocation dynamics, allows us to determine the presence of an analyte. We have developed software to automatically sort and analyse each event resulting in a workflow of <90 minutes (Figure 1B).

Our study shows that quantitative multiplexed detection of 40miRNAs is possible using our platform. In addition, we can simultaneously detect miRNA, protein and small molecules. Finally- we show multiplexed detection of 40 miRNAs, associated with cardiac fibrosis, directly from human serum.



05 Kavitha Vimalesvaran
k.vimalesvaran@imperial.ac.uk

The ratio of SSFP blood signal ratio between the ascending aorta and left ventricle predicts aortic stenosis severity: a retrospective analysis

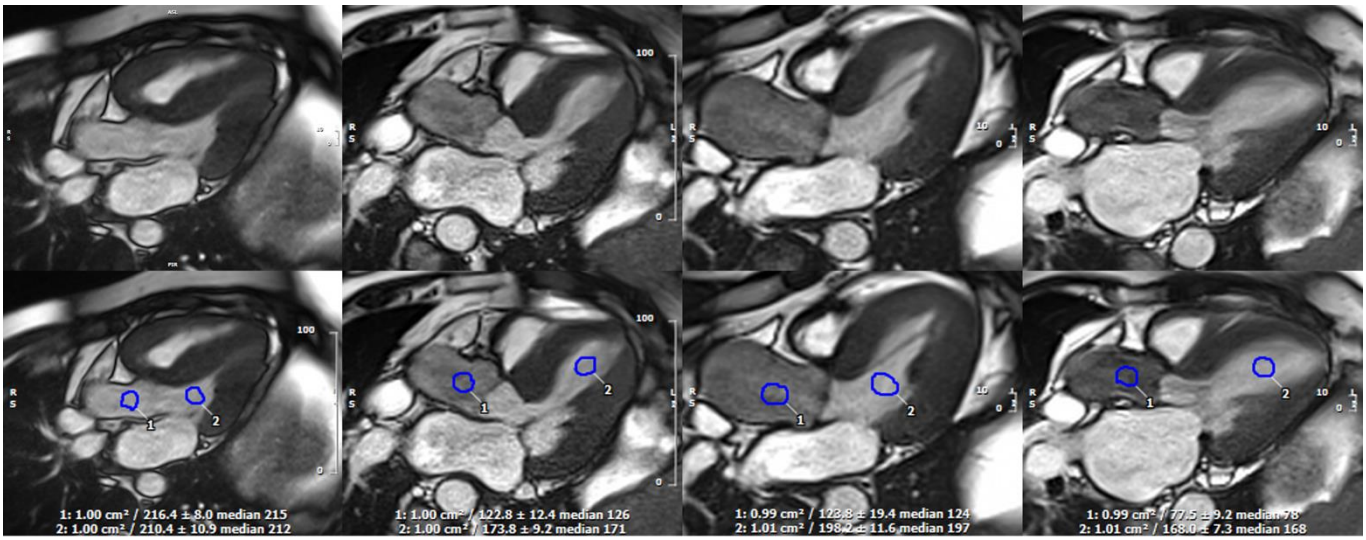
Kavitha Vimalesvaran[1], Sameer Zaman[1], James Howard[1], Marta Varela[1], Fatmatulzehra Uslu[3], Ben Ariff[1], Nick Linton[2], Anil Bharath[2] and Graham Cole[1]
[1] National Heart and Lung Institute; [2] Bioengineering Department, Imperial College London; [3]Bursa Technical University, Turkey

Aortic stenosis (AS) is the most common valvular heart disease, with prevalence increasing with age. Cardiovascular magnetic resonance (CMR) imaging is an important tool for evaluating AS, co-existing aortic disease, and concurrent myocardial abnormalities. This study aimed to investigate whether the low signal on cine imaging correlated with existing gold-standard echocardiographic biomarkers of AS severity.

A single-center retrospective analysis was conducted on 214 patients with aortic stenosis undergoing cardiac MRI and echocardiography for clinical reasons. The signal intensity was measured in the aorta and left ventricle (LV) in a 3-chamber cine view at end-systole. The ratio of mean signal intensity in the aorta to the LV (Ao:LV) was used to compare against gold-standard echocardiographic parameters, including dimensionless index (DI) and aortic valve maximum velocity (Vmax), using the Pearson correlation coefficient.

The 214 patients (median age 68, 62% male) included no AS (n=63), mild AS (n=44), moderate AS (n=48), and severe AS (n=59) according to echocardiography. There was a strong correlation between the blood Ao:LV ratio of SSFP signal with Vmax (R=-0.832) and DI (R=0.764). A ratio of >0.87 was 90% sensitive and 83% specific for ruling out aortic stenosis as defined by the final echocardiography diagnosis.

In conclusion, the Ao:LV ratio derived from a SSFP 3-chamber cine image has a strong correlation with aortic stenosis severity measured using echocardiography. This simple measurement may help identify patients who require further specialised aortic valve imaging, potentially allowing inline identification and adaptive image acquisition.



TOPIC 2	TRANSLATING RESEARCH TO CLINICAL PRACTICE

ORAL PRESENTATIONS

Simone Hadjisymeou Andreou
s.hadjisymeou-andreou22@imperial.ac.uk

Is sputum Galactomannan a feasible screening test for Aspergillus infection in Paediatric Cystic Fibrosis patients?

S. Hadjisymeou Andreou[1,2], C. Lanfranchi[2,3], S. Salenian[1,2], N. Ramadan[2], A. Jones[2], J. C. Davies[1,2] and R. Pabary[2]
[1] National Heart and Lung Institute; [2] Royal Brompton and Harefield Hospitals, Guy's and St. Thomas' NHS Foundation Trust; [3] Università degli studi di Milano, Italy

Aspergillus fumigatus (AF) is a common respiratory tract infection in children with cystic fibrosis (CF), with early detection being important to prevent lung damage. Fungal culture is the gold standard for diagnosing AF, but it can underestimate its presence. Galactomannan (GM) antigen testing in serum and bronchoalveolar lavage is well established in detecting invasive AF infection. The study aimed to determine if sputum GM could detect AF even when cultures are negative and shorten the time-to-treatment compared to culture.

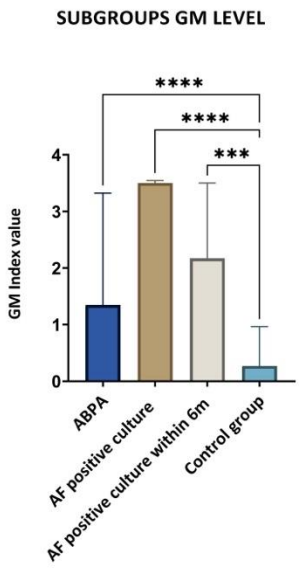


Figure 1 Columns show median and error bars interquartile range. P value was calculated by Kruskal-Wallis test comparing GM values between the different groups. P < 0.05 was considered significant.

The study prospectively analysed sputum GM in paediatric CF patients from December 2019 to September 2022. AF infection was confirmed on extended fungal culture, and a GM index (GMI) value of ≥0.5 was considered reactive.

The study analysed 550 sputa from 161 patients. AF was cultured in 18 sputa from 11 patients (7% prevalence). GMI was reported sooner than culture, and GMI was significantly higher in all three AF groups (allergic bronchopulmonary aspergillosis, AF-positive culture time 0, AF positive within 6 months) compared to controls p< 0.0001 (Figure 1). GMI was elevated in non-AF fungi positive culture but significantly lower than in AF positive culture. Antifungal therapy led to a decrease in GMI and an improvement in FEV up to 6 months after treatment.
The study concludes that sputum GM is elevated in CF children with ABPA and AF positive cultures, and it shows promise as a biomarker of infection in assessing treatment response. However, sputum GM is not entirely specific, indicating an overlap with control and non-AF positive fungal cultures.

Niamh Errington
n.errington@imperial.ac.uk

Diagnostic miRNA signatures for treatable forms of pulmonary hypertension highlight challenges with clinical classification

Niamh Errington[1,2], Sokratis Kariotis[1,3,4], Christopher J Rhodes[1], Emmanuel Jammeh[3], Yiu-Lian Fong[5], Zhou Lihan[6], Cheng He[6], Timothy Jatkoe[5], Tatiana Vener[5], John Wharton[1], A A Roger Thompson[2,7], Robin Condliffe[2,7], David G Kiely[2,7], Luke S Howard[1,8], Eileen Harder[9], Aaron Waxman[9], Mark Toshner[10,11], Dennis Wang[1,4], Allan Lawrie[1] and Martin R Wilkins[1]
[1] National Heart & Lung Institute; [2] Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield; [3] Department of Neuroscience, University of Sheffield; [4] Singapore Institute for Clinical Sciences, A*STAR Research Entities; [5] Janssen Pharmaceutical Companies of Johnson & Johnson; [6] MiRXES Lab, Singapore; [7] Sheffield Pulmonary Vascular Disease Unit, Sheffield Teaching Hospitals Foundation Trust; [8] Imperial College Healthcare NHS Trust; [9] Brigham and Women's Hospital and Harvard Medical School, USA; [10] Papworth NHS Foundation, Cambridge; [11] Department of Medicine, University of Cambridge

Background: The five current classification groups for patients with pulmonary hypertension (PH) cover an expansive range of disease phenotypes. We aimed to measure and compare circulating miRNA levels in 1484 patients to identify molecular signatures associated with the different clinical groups.

Methods: Serum samples from 1484 patients; 1150 with PH and 334 breathless disease controls were assayed for 650 miRNAs, using miRNA specific RT-PCR. Following quality control and batch correction, 326 well-quantified miRNAs were analysed with machine learning models to identify signatures for PH from disease controls, as well as for subgroups of PH. We also took an unsupervised approach (spectral clustering), clustering patients with pulmonary arterial hypertension (PAH), PH-left heart disease (PH-LHD), and patients with PH-lung agnostically to classification group.

Results: Panels of 9 miRNA outperformed NT-proBNP at detecting PH, as well as identifying PAH (AUC 0.69) and chronic thromboembolic pulmonary hypertension (CTEPH), AUC 0.70). The miRNA PAH signature was validated in an external cohort of patients of 55 patients with PAH and 158 disease controls. However, the signature was also detected in some patients with PH-LHD and PH-lung, implying either intersecting pathology, or misclassification. To investigate this, we took an unsupervised approach of a mixed cohort (PAH, PH-LHD and PH-lung) and identified 6 distinct patient subgroups. These subgroups had differences in survival (HR 1.77 and 1.71 for clusters with poor survival), clinical features, and pathway enrichment.

Conclusions: Circulating miRNAs may have diagnostic merits in addition to identifying groups of patients with shared biological processes and pathways.

Jakob Jonnerby
l.jonnerby21@imperial.ac.uk

Viral RNA decline time predicts transmission of SARS-CoV-2 and Influenza A

Jakob Jonnerby[1], Seran Hakki[1], Joe Fenn[1], Jie Zhou[2], Anika Singanayagam[2], Kieran J Madon[1], Aleksandra Koycheva[1], Christine Kelly[3], Hamish Houston[1], Sean Nevin[1], Rhia Kundu[1], Shazaad Ahmad[4], Nieves Derqui-Fernandez[1], Emily Conibear[1], Graham P Taylor[2], Neil Ferguson[5], Maria Zambon[6], Wendy S Barclay[2], Jake Dunning[7], Benjamin J Cowling[8], Li Ka Shing[9] and Ajit Lalvani[1]
[1] National Heart and Lung Institute; [2] Department of Infectious Disease, Imperial College London; [3] Centre for Experimental Pathogen Host Research, University College Dublin, Ireland; [4] Department of Virology, Manchester Foundation NHS Trust; [5] NIHR Health Protection Research Unit in Modelling and Health Economics, MRC Centre for Global Infectious Disease Analysis, Jameel Institute; [6] National Infection Service, UK Health Security Agency; [7] NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, University of Oxford; [8] WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health; [9] Faculty of Medicine, The University of Hong Kong

The development of transmission-blocking vaccines and therapeutics against respiratory viruses such as Influenza and SARS-CoV-2 depend on understanding biomarkers that are predictive of the risk of transmission.

We show that the viral RNA decline time, the time for the viral load to reduce by a factor of e, correlates with transmission of both Influenza A and SARS-CoV-2, based on analysis from two prospective community transmission studies where URT samples were collected longitudinally from PCR-confirmed index cases and their contacts between 2020-2021 (SARS-CoV-2, N=38 index cases and N=69 contacts) and 2008-2012 (Influenza A, N=199 index cases and N=604 contacts).

Bayesian beta-binomial regression showed strong evidence of an increase in the secondary attack rate from SARS-CoV-2 index cases with longer decline times (posterior probability (pp) of a positive association=0.94). The effect size was found to be 37% (95% CrI -10%, 94%) estimated as the relative increase in the SAR for a decline time one standard deviation above the cohort mean.

In Influenza A cases, strong evidence was also found of an increase in transmission risk from cases with slower viral RNA decline times (pp=0.9). Here, the effect size was found to be a 30% (95% CrI -6%, 75%) increase in the SAR for a decline time one standard deviation above the cohort mean.

These findings show for the first time an association between prolonged viral shedding and an increase in transmission risk and highlight the importance of interventions to reduce the duration of viral load shedding, such as antiviral treatment and vaccination.

Dario (Roberto) Sesia
r.sesia22@imperial.ac.uk

Predicting All-Cause Mortality and Acute Coronary Syndrome Risk Using Machine Learning

D. Sesia[1], W Xuan[1], A. Mulla[1], B. Glampson[1], D. Papadimitriou[1], A. Shah[1], E. Meyer[1], Galasko[2], C. Herbert[3], J. Townend[4], S. Grant[5], T. Johnson[6], I. Squire[7], N. Curzen[8], K. O'Gallagher[9], A. Shah[9], R. Kharbanda[10], R. Patel[11], D. Perera[12], K. Channon[10], C. H. Yap[1], A. Kaura[1] and J. Mayet[1]

[1] Imperial College Healthcare NHS Trust; [2] Blackpool Teaching Hospitals NHS Foundation Trust; [3] Leeds Teaching Hospitals NHS Trust; [4] University Hospitals Birmingham NHS Foundation Trust; [5] South Tees Hospitals NHS Foundation Trust; [6] University Hospitals Bristol NHS Foundation Trust; [7] University Hospitals of Leicester NHS Trust; [8] University Hospital Southampton NHS Foundation Trust; [9] King's College Hospital NHS Foundation Trust; [10] Oxford University Hospitals NHS Foundation Trust; [11] University College London Hospitals NHS Foundation Trust, London; [12] Guy's & St Thomas' NHS Foundation Trust

Introduction: Clinical prediction models have the potential to positively impact clinical decision making and subsequent patient outcomes. We utilised machine learning to predict the risk of acute coronary syndrome (ACS) and all-cause mortality amongst consecutive patients admitted across five hospitals who underwent a troponin test on admission.

Methods: We used the NIHR Health Informatics Collaborative dataset of 257,948 patients who underwent troponin testing across five centres between 2010 and 2017. Comorbidities were determined using ICD-10 diagnostic codes. Five base models and a neural network were trained using a 70:15:15 dataset split across training, validation, and testing.

Results: The study cohort consisted of 47,688 admitted patients who underwent blood tests within 24 hours. The one-month and inpatient mortality rates were 7.44% and 6.26%, respectively, and 6.29% had ACS. Age, troponin level, haemoglobin, creatinine, white cell count, platelet count, and sodium had the strongest correlation with mortality. Gender and ethnicity, had minimal impact on model performance. Amongst all the comorbidities, hypertension had the highest input feature importance on model prediction. The Random Forest achieved an AUC, accuracy, precision, and recall of 0.90, 0.92, 0.78, and 0.11, respectively. In comparison, the widely used HEART score yielded values of 0.75, 0.71, 0.65, and 0.65. The final neural network outperformed all base models and the HEART score, with respective values of 0.90, 0.93, 0.92, and 1.0.

Conclusion: The neural network prediction model developed provides a reliable and robust predictor of mortality risk, with the potential to improve treatment decisions and patient outcomes in clinical practice.

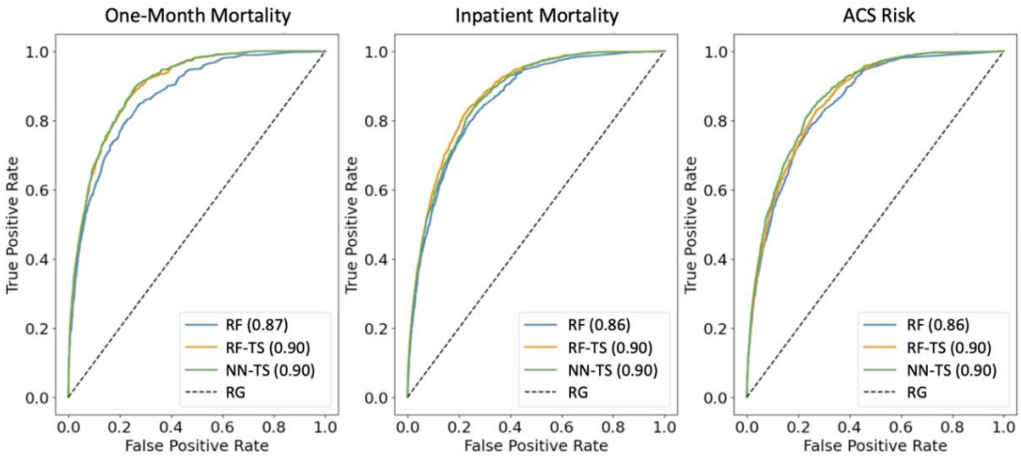


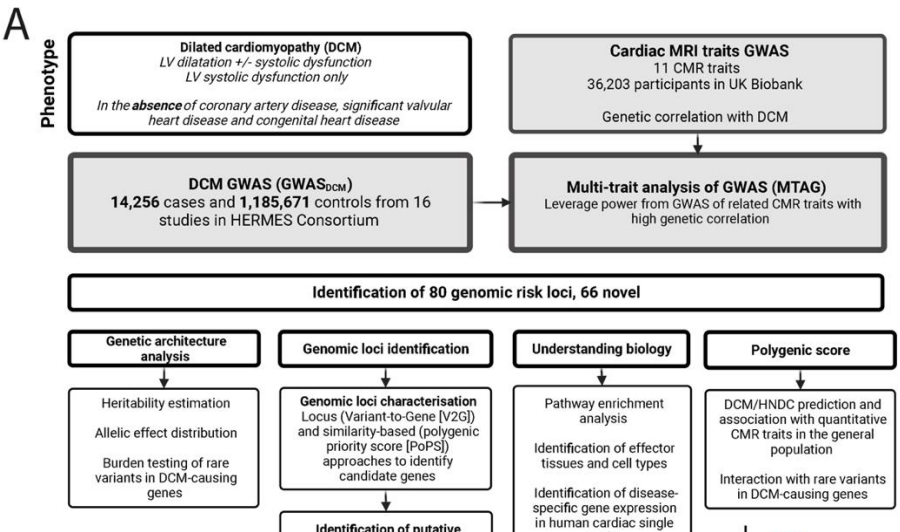
Figure 1 – ***Roc (Receiver Operating Characteristic) Analysis of One-Month Mortality, Inpatient Mortality and ACS Risk: Discriminating Power of Admission Troponin, Comorbidities, and Additional Blood Tests in Predicting Risk.*** *RF, Random Forest; -TS, Tuned to best hyperparameters and sensitive features; NN, Neural Network; RG, Random Guess.*

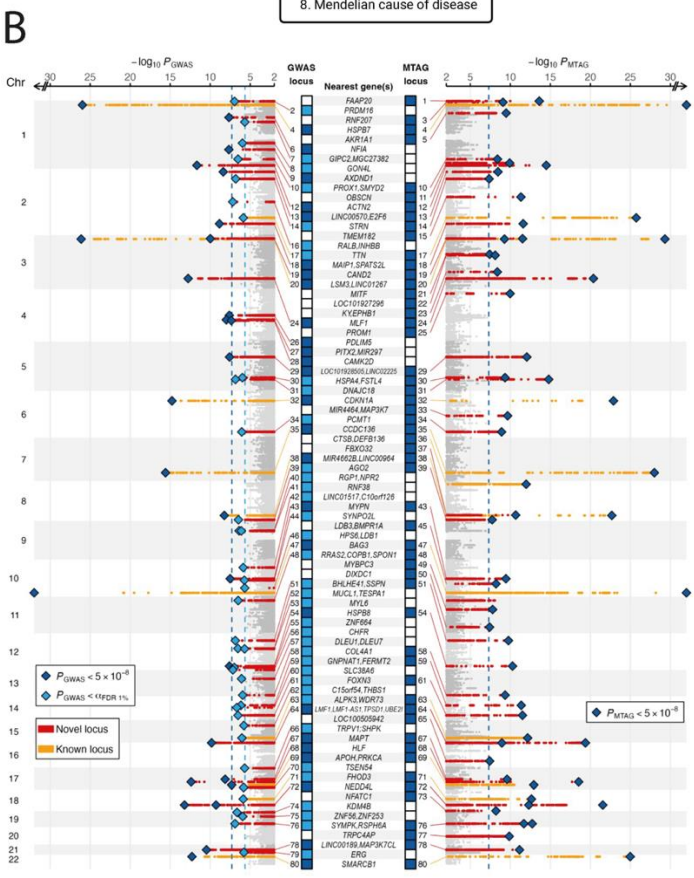
FLASH PRESENTATIONS

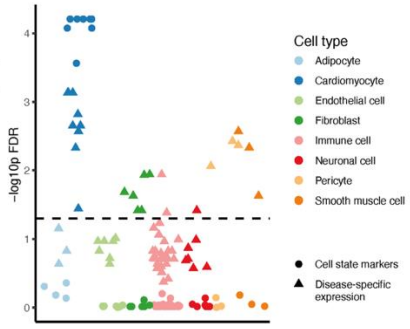
06 Sean Zheng
sean.zheng17@imperial.ac.uk

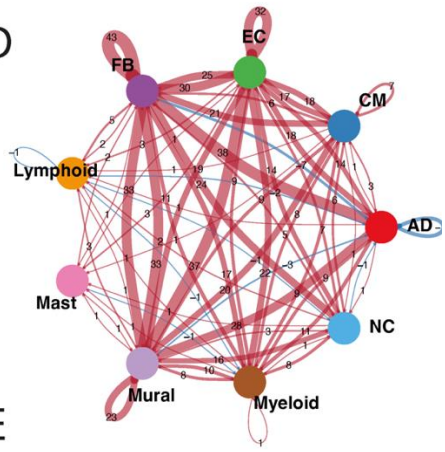
Large-scale genome-wide association study in over one million participants highlight insights in genetic architecture and cellular biology in dilated cardiomyopathy

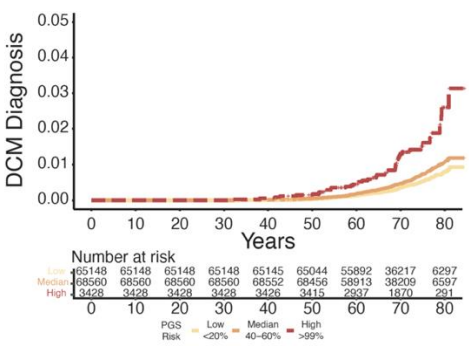
Sean L Zheng[1], Albert Henry[2], Michael Lee[1], Isabelle Bond[2], Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) Consortium, Michela Noseda[1], James Ware[1] and Tom Lumbers[2]
[1] National Heart and Lung Institute; [2] Institute of Health Informatics, University College London











Dilated cardiomyopathy (DCM) is a leading cause of heart failure. Although several genes are established Mendelian causes of DCM, many have no identifiable genetic cause. To bridge the gap in our understanding of the genetic basis of DCM, we performed the largest DCM GWAS with 14,256 cases and 1,185,671 controls from 16 studies from the HERMES Consortium, and improved genetic discovery by incorporating genetically-correlated imaging-derived cardiac functional traits (left ventricular end-systolic volume, circumferential strain, and ejection fraction) through multi-trait analysis of GWAS (Figure 1A). In total, there were a total of 80 independent loci, with 65 being novel (genetic heritability 11%) (Figure 1B). Using a two-step locus prioritization approach synthesizing evidence from 8 functionally-informed prediction models, we identify 64 candidate genes, with pathway enrichment highlighting sarcomeric and cytoskeletal function, cellular adhesion and junction organisation, unfolded protein response, and Wnt and TGF-beta signaling. Incorporation of single nuclei transcriptomics of 52 DCM and 18 controls identified heritability enrichment in disease-specific expression profiles of cardiomyocytes, fibroblasts and mural cells (Figure 1C), with analysis of intercellular communication highlighting the importance of paracrine signaling in DCM (Figure 1D). Rare variant burden testing of candidate genes across two cohorts (UK Biobank and 100,000 Genomes Project) identified several novel DCM-causing genes, including MAP3K7 and SSPN. Finally, we generated a polygenic score (PGS) with over 4 million SNP predictors that associates with DCM in 347,585 unrelated participants of White British ancestry in UKB (OR per PGS SD 1.8, P<2x10-16; top centile vs. median OR 3.8, P 2x10-10) (Figure 1E).

07 Benjamin Fletcher
benjamin.fletcher19@imperial.ac.uk

Investigating the Roles of miR-424 and miR-542 in Muscle Atrophy

Benjamin Fletcher[1], Paul Kemp[1] and Scott Bowen[2]
[1] National Heart & Lung Institute; [2] School of Biomedical Sciences, University of Leeds

Disease associated muscle wasting reduces quality of life and increases mortality. Wasting occurs as muscle proteolysis and protein synthesis and increased and decreased, respectively, to provide nutrients for the immune response. In many conditions, despite symptoms being alleviated, wasting continues as the underlying disease is not cured. A better understanding of this wasting is required to identify therapeutic targets.

We identified miR-424 and miR-542 as potential central regulators of muscle wasting in COPD, ICU acquired weakness and aortic surgery patients. Quadriceps expression of these miRNAs associated with markers of disease severity: TLco in COPD; SOFA in ICUAW; LVEF in aortic surgery. In cells, and mice, these miRNAs reduced protein synthesis and promoted mitochondrial dysfunction, whilst the over-expression of either promoted muscle loss.

Here, we compared the expression of miR-424 and miR-542 with the transcriptome of quadriceps biopsies both before and after surgery. We also compared the expression of these miRNAs in the skeletal muscle of 4 groups: controls; diabetics; heart failure patients; diabetics with heart failure.

Comparing the transcriptome with miR-424 and miR-542 showed both to negatively associate with oxidative phosphorylation. Furthermore, pre-surgery miR-542-5p expression negatively associated with myogenesis and positively associated with MYC regulated genes. Quadriceps expression of these miRNAs was elevated in all three of the disease groups and negatively associated with heart function (LVEF).

These data show that the expression of miR-424 and miR-542 is elevated in response to a range of conditions and that these miRNAs modulate gene expression in a manner consistent with muscle wasting.

08 Parris Williams
parris.williams@imperial.ac.uk

Immediate smoking cessation support during lung cancer screening: long term outcomes from two randomised controlled trials

Parris J Williams[1,2,3], Keir EJ Philip[1,2], Sara Buttery[1,2], Alexis M Perkins[1,2], Ley Chan[1,3], Emily C Bartlett[3], Anand Devaraj[1,3], Samuel V Kemp[3], Jamie Addis[3], Jane Derbyshire[4], Michelle Chen[4] Michael Polkey[3], Anthony A. Laverty[5], Nicholas S Hopkinson[1 2].

[1] National Heart and Lung Institute; [2] NIHR Imperial Biomedical Research Centre, Imperial College London; [3] Royal Brompton and Harefield Hospitals; [4] RM Partners, West London Cancer Alliance; [5] Public Health Policy Evaluation Unit, School of Public Health, Imperial College London

Background: Immediate smoking cessation interventions delivered alongside targeted lung health checks (TLHC) to screen for lung cancer have been shown to increase abstinence rates at three months in this high-risk population, but longer-term impact remains to be established.

Methods: We followed up participants from two randomised controlled trials in people aged 55 to 75 years who smoked and took part in a TLHC. These compared usual care (signposting to smoking cessation services) to an offer of immediate smoking cessation support including pharmacotherapy; in the QuLIT1 trial this was delivered face to face, in QuLIT2 it was delivered remotely. Follow-up was conducted 12 months after intervention delivery and consisted of a short telephone interview and subsequent biochemical verification of smoking cessation using exhaled CO.

Results: 430 (115 in QuLIT1 315 in QuLIT2) people were enrolled initially. There were 4 deaths before 12 months leaving 426 [62.1± 5.27 years old and 48% female] participants for analysis. At 12 months those randomised to the smoking cessation intervention had significantly higher quit rates compared to usual care both for self-reported 7-day point prevalence (20.0% vs 12.8%; AOR= 1.78 95% CI, 1.04-2.89) and CO verified quits (12.1% vs 4.7%; AOR= 2.97 95% CI, 1.38-6.90). Those in the intervention arm were also more likely to report having made a quit attempt (45.0% vs 28.9% respectively: AOR= 1.90, 95% CI 1.15-3.15), all logistic regression models were adjusted for age, sex, deprivation and QuLIT trial.

Conclusion: Providing immediate smoking cessation alongside targeted lung health checks increases long-term, biochemically confirmed smoking abstinence.

09 Fama Manneh

f.manneh21@imperial.ac.uk

Development of an enhanced charged novel superhydrophobic haemostatic device

Fama Manneh, Chengxin Lian, Choon Hwai Yap and Mike Emerson
National Heart and Lung Institute

Background: Trauma causes nearly 6 million deaths annually. Early haemostatic intervention can prevent over 25% of post-traumatic haemorrhagic deaths. However, current haemostatic patches lead to blood loss and risky dressing removal. Our lab has identified clot-inducing, superhydrophobic nanofibers that allow easy post-clot removal. We aim to enhance nanofiber haemostatic properties by adding surface charges, which can impact platelet and intrinsic pathway activation.

Aim: To enhance the platelet and intrinsic pathway activation ability of our nanofibers through the addition of surface charges.

Materials and methods: Serotonin ELISA (enzyme-linked immunosorbent assay) was conducted to assay for platelet activation, light transmission aggregometry was conducted to measure platelet aggregation, and calibrated automated thrombography (CAT) assessed coagulation potential. Grafting of charged groups to nanofibers was performed via etching with oxygen and ammonia plasma for negative and positive charges, respectively. A zeta sizer was used to confirm the charges.

Results: Light transmission showed no effect on platelet aggregation up to 1mg/ml of nanofibers. Serotonin secretion was significantly increased for samples treated with 0.25mg/ml and 1mg/ml nanofibers compared to untreated. The CAT assay exhibited higher thrombin generation in nanofiber-treated platelet-poor plasma. Oxygen-etched nanofiber's zeta potential was ~-39, while uncharged was ~-27, confirming our grafting methodology.

Conclusion: In summary, uncharged nanofibers induced thrombin generation and serotonin secretion, indicating coagulation and platelet activation. Additionally, negative surface charges were confirmed. In future, assays will

be repeated with the charged nanofibers and extended to pre-clinical models to develop new haemostatic devices and potentially improve outcomes and pre-hospital survival.

TOPIC 3	EXPERIMENTAL MODELS OF DISEASE

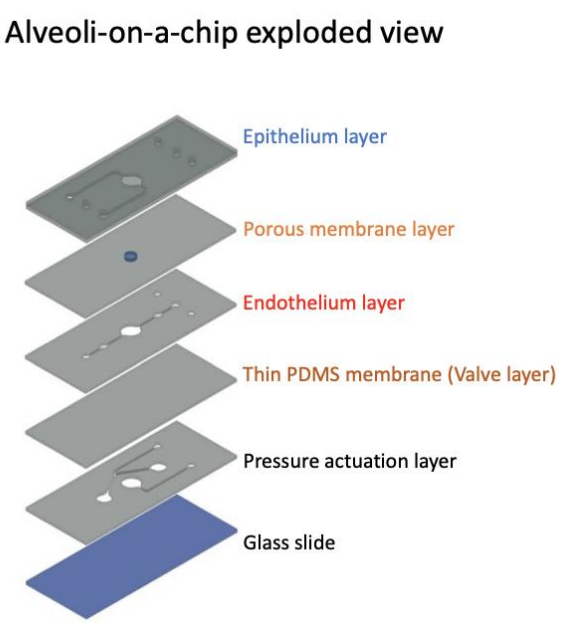
ORAL PRESENTATIONS

Jenny Katsouli
j.katsouli21@imperial.ac.uk

Alveoli-on-a-chip integrated onto a fluorescence microscope to direct observe pathophysiological mechanisms

Jenny Katsouli[1], Joseph Xavier[1,2] and Jorge Bernardino de la Serna[1]
[1] National Heart and Lung Institute; [2] Sree Chitra Tirunal Institute for Medical Sciences & Technology, India

There is a need to develop more complex 3D tissue models to recapitulate distal airways microphysiology. It is envisioned, that organ-on-a-chip technology will resolve mechanistic biomedicine and pharmacology research; and in the clinic, will inform about personalised dose and adverse outcome pathways. Our alveoli-on-a-chip (AOC) aims to investigate the anthropogenic exposome in health, toxicology and disease, and shed light to pharmacological treatments. We have recapitulated the alveolar niche by creating a modular, customizable design to quick and cost-effectively produce a complex AOC; which integrates alveolar breathing dynamics, flows and pressures. We employed xurography for our 4-layered molds, casted using PDMS and plasma bonded. The endothelial and epithelial chambers are separated by an ultra-thin collagen membrane resembling the basal lamina, and two further intercalated layers serve as valves to replicate pneumonic pressures. We validated our model and characterized its permeability, and translocation properties with and without cells. Our model comprise human alveolar type 1 (hAELVi) and umbilical cord vein endothelial (HUVEC) cells intercalated by a collagen membrane (<10 □m). Using piezoelectric-driven microfluidics, a continuous flow is introduced at the endothelial side. Additionally, air pressure applied asynchronously on to our 2 dedicated independent channels generate pneumonic forces and stretching on the cells supported and interconnected at the collagen coated grid, which resembles alveolar dynamics during inhalation and exhalation. Finally, our AOC is integrated onto a high resolution fluorescence microscope to resolve molecular mechanisms involved during exposure of bio and inert matter; our optically-inert chips allow direct observation of fluorescently labelled biosensors.



Dana E. Al-Ansari
d.al-ansari21@imperial.ac.uk

Biomaterial-Driven 3D in vitro Spheroid-Based Lymphangiogenesis Model Using Click Crosslinked Hydrogels

Dana Al-Ansari[1,2], Hu Yang Yangshuo[2], Nicola Contessi Negrini[2], Daniela Pirri[1], Adam Celiz[2] and Graeme M. Birdsey[1]
[1] National Heart and Lung Institute; [2] Department of Bioengineering, Imperial College London

Despite recent advances in understanding the molecular mechanisms of lymphangiogenesis, most studies use conventional 2D cell culture, which is limited by unconstrained cell migration and x–y plane adhesion. In contrast, 3D cell culture replicates the tissue microenvironment and cellular responses by enhancing cell–extra cellular matrix interactions. We established a 3D in vitro lymphangiogenesis model using bioorthogonal click-crosslinked gelatin hydrogels (GelTN). The mechanical properties and cytocompatibility of GelTN (6 - 12% w/v) were assessed for optimised encapsulation of lymphatic endothelial cells (LECs). To model lymphangiogenesis, LEC spheroids were generated and embedded in GelTN hydrogel (+/- VEGF-C) followed by quantifying number and length of

LECs emerging from spheroids. The optimised model was tested in several applications, including siRNA gene inhibition and modelling patient-derived endothelial colony forming cells. Overall, GelTN demonstrated tuneable mechanical properties (E = 1-6 kPa), gelation times (2-15 min) and biodegradability. The viability and metabolic activity of LECs were preserved by GelTN at concentrations < 12%. An inhibitory influence of matrix stiffness on LECs network and marker genes expression (PROX1, LYVE1 and VEGFR3) was observed at concentrations > 8%. At 6% GelTN, the lymphangiogenic activity of LEC spheroids showed VEGF-C dependent sprouting. Our data showed the robust nature of the 3D lymphangiogenesis model, which can be used as an in-vitro platform for assays with wide applicability. In addition, the tuneable mechanical properties of GelTN provide an avenue not only for tissue engineering but also for clinical applications such as cell- or growth factor-incorporated hydrogels for targeted therapy.

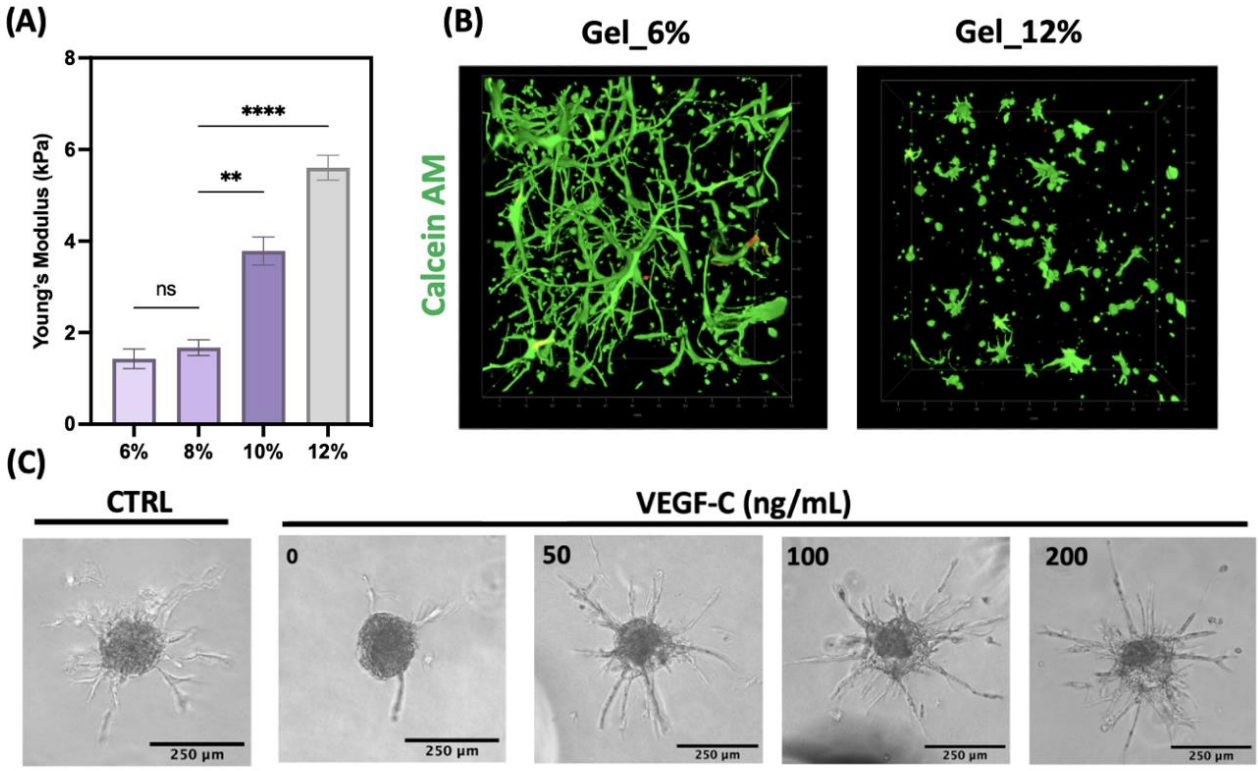


Figure 1. (A) *Young's Modulus of Gelatin_Tz/Nb at different concentrations.* ***(B)*** *Top view of Z-stack images of lymphatic endothelial cell (LECs) network formation in 6% vs 12% after 2 weeks of encapsulation.* ***(C)*** *Brightfield images of LECs spheroid – laden Gelatin-Tz/Nb at 6% (+/-) VEGF-C.*

Ciara Campbell
Ciara.campbell20@imperial.ac.uk

Altered airway epithelial cell function in children with severe asthma following co-exposure with repeated HDM and Respiratory Syncytial Virus

Ciara Campbell, Helen Stölting, Mindy Gore, Katie Bonner, Elizabeth Scotney, Clare M. Lloyd and Sejal Saglani
National Heart and Lung Institute

Airway epithelial cells are critical for primary immune and barrier defence against environmental exposures such as pathogens and allergens. Most children with severe asthma are sensitised to the perennial aeroallergen house dust mite (HDM). In vitro studies investigating epithelial function in response to HDM and/or virus have only used single exposures, however, persistent allergen exposure with superimposed viral infection better represents acute asthma exacerbations.

We mimicked this co-exposure of HDM with a subsequent infection of respiratory syncytial virus (RSV) in airway epithelial cells grown at air-liquid interface from preschool and school-aged children with severe asthma and aged matched healthy controls.

While a single dose of HDM did not alter epithelial immune responses either at baseline or after RSV infection, recurrent HDM exposure decreased interferon (IFNB1 & IFNL) responses to RSV, particularly in PSW donors. Bulk RNA-sequencing of cell lysates at 72H after RSV infection identified 35 genes downregulated in response to recurrent HDM including MMP9, CSF2 and genes involved in barrier integrity (DSC2, ECM1, LAMC2). Gene expression of MMP9 was decreased by 10-fold when exposed to repeated HDM in preschool asthma. RNA-sequencing analysis also confirmed dampened IFN-signalling following RSV infection in cells repeatedly exposed to HDM, which may contribute to a reduced ability to clear pathogens.

These results suggest that recurrent exposure to HDM suppresses antiviral responses, particularly in cells from preschool children with asthma, which may result in reduced viral clearance and contribute to reduced barrier integrity.

FLASH PRESENTATIONS

10 Zuzanna Jablonska
zuzanna.jablonska19@imperial.ac.uk

The secretome of cardiac mesenchymal stromal cells protects human cardiomyocytes from in vitro ischaemia-reperfusion injury

Zuzanna Jablonska[1], Yue Qin[1], Michael D. Schneider[1,2] and Michela Noseda[1,2]
[1] National Heart and Lung Institute; [2] British Heart Foundation Centre of Research Excellence, Imperial College London

Background: Myocardial infarction remains one of the main causes of death worldwide, despite undeniable progress in reperfusion strategies. However, these do not reverse the molecular damage that has already occurred. Preventing cardiomyocyte loss is an important therapeutic target, as infarct size predicts the risk of heart failure and one-year all-cause mortality. Here, the protective role of the secretome derived from cardiac mesenchymal stromal cell (cMSC) was tested in a novel in vitro model of ischaemia-reperfusion injury.

Methods: Metabolically mature hiPSC-CMs were obtained according to a recent protocol by Feyen et al. Time-course experiments were carried out followed by the analysis of hiPSC-CM cell death in response to hypoxia-reoxygenation, in the presence and absence of cMSC conditioned media. Finally, a novel proximity biotinylation strategy using TurboID was implemented to carry out mass spectrometry profiling of the cMSC secretome to characterise protective mediators.

Results: A significant increase in cell death of mature hiPSC-CMs was observed in response to hypoxia in combination with nutrient deprivation, when compared to standard hiPSC-CMs. The addition of reoxygenation following hypoxia resulted in even greater extent of cell death. Notably, cMSC conditioned medium added at the time of reoxygenation significantly reduced hiPSC-CM cell death. Proteomics of the cMSC secretome identified 44 putative mediators of the observed cardioprotection.

Conclusions: A novel in vitro model of ischaemia-reperfusion injury was developed using metabolically mature hiPSC-CMs and hypoxia-reoxygenation. This was successfully employed for testing cMSC-mediated cardioprotection. Using an elegant proximity biotinylation strategy, 44 secreted putative mediators of the protective effect were identified by mass spectrometry.

11 Anthony Sinadinos
a.sinadinos@imperial.ac.uk

F/HN-pseudotyped lentiviral vector-mediated transduction of non-human primates

A. Sinadinos[1], U. Griesenbach[1], G. McLachlan[2,] C. Cheminay[3], J. Ashour[3], C. Meng[1], E. Castells[4], R. Dean[4], MA. Viegas[4], AC. Boyd[5], JC. Davies[1], DR. Gill[4], SC. Hyde[4], D. Blanset[3] and EWFW. Alton[1]
[1] National Heart and Lung Institute; [2] The Roslin Institute, University of Edinburgh; [3] Boehringer Ingelheim Pharmaceuticals Inc, USA; [4] Radcliffe Department of Medicine, University of Oxford; [5] Centre for Genomic and Experimental Medicine, University of Edinburgh

Objectives: We have developed a lentiviral vector platform pseudotyped with the Sendai virus F and HN envelope proteins (rSIV.F/HN), including the clinical candidate BI 3720931 for cystic fibrosis (CF) gene therapy. Previously,

we demonstrated efficacy in CF-patient bronchial epithelial cell air–liquid interface cultures and intestinal organoids, as well as efficient and persistent in vivo transduction of murine airways. Here we assess transduction efficiency and acute toxicology in non-human primates (NHPs).

Methods: Male cynomolgus monkeys received a single dose of rSIV.F/HN vector expressing green fluorescent protein (GFP) (4.2e9 transduction units) or placebo via an endotracheal tube (n=3/group), achieving lung deposition of ~25%. Toxicology was assessed by histopathology, clinical pathology, cytokine levels and changes in body and organ weight; transduction efficiency was quantified by GFP immunohistochemistry and vector-specific mRNA 7 days post dosing.

Results: There were no vector-related clinical observations, mortality, or changes in body or organ weight. Clinical pathology and cytokine analyses were unremarkable. Minimal mixed-cell centriacinar inflammation was observed in 1/3 active-treated animals. Airway epithelial cell transduction efficiency was 9–12% and vector-specific mRNA levels were ~45x endogenous cystic fibrosis transmembrane conductance regulator mRNA levels.

Conclusions: This study extends our findings of rSIV.F/HN-based in vivo gene transfer in mice to NHPs, demonstrating transduction efficiency in the range likely to relate to clinical benefit, without toxicity. Animals treated with a higher dose are currently being analysed. These data, together with our previous murine data, support further progression of BI 3720931 towards the clinic.

12 Maike Haensel
maike.haensel18@imperial.ac.uk

Microfluidic platform for modelling of alveolar-vascular cell interactions in pulmonary hypertension (PH) associated with chronic obstructive pulmonary disease (COPD)

M. Haensel[1], V. Ho[1], J. Edel[2], D. Overby[3], C. Lloyd[1] and B. Wojciak-Stothard[1]
[1] National Heart and Lung Institute; [2] Department of Chemistry; [3] Department of Bioengineering, Imperial College London

Introduction: Progressive thickening of intrapulmonary arterioles in PH restricts blood oxygenation. It is an important complication in COPD. Conventional cell culture methods do not accurately mimic human physiology. Organs-on-chips enable key structural and functional features of human organs to be replicated for in-vitro disease modelling.

Aim: To develop an organ-on-a-chip for co-culture of human pulmonary artery endothelial cells with small airway epithelial cells, smooth muscle cells, pericytes and fibroblasts under basal and disease conditions.

Methods: REspiratory-and-VAScular-on-a-chip (REVAS) was designed with overlayed top and bottom microfluidic channels hosting alveolar and vascular cells, separated by a porous membrane. In silico simulation of flow and pressure within the REVAS circuit was performed with COMSOL Multiphysics. Cell morphology, differentiation markers and cell function were studied.

Results: Simulation of air flow (1 dyne/cm2) through respiratory channels and media flow (4 dynes/cm2) through vascular channels confirmed physiological range of pressure, flow pattern and wall shear stress. Flow-stimulated endothelial cells grown in top channels showed 3-fold increase in cell alignment, compared with static controls (n=3). Epithelial, endothelial, smooth muscle cells, fibroblasts and pericytes expressed tissue-specific differentiation markers in long-term (9 days) culture. Interactions of endothelial cells with other vascular cell types significantly enhanced endothelial barrier function under basal conditions and following stimulation with thrombin (1U/mL, 1hr).

Conclusion: REVAS incorporates multiple cell types from the respiratory and vascular systems. This 3D co-culture platform, validated under flow and static conditions, can potentially be used for in vitro disease modelling and towards personalised medicine.

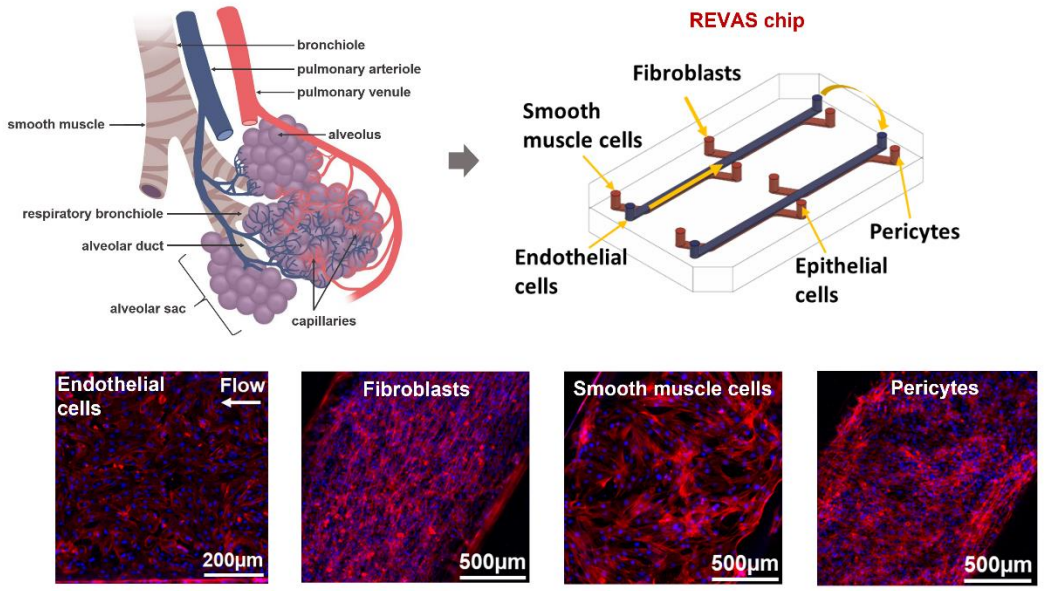


Figure: REVAS-on-a-chip including top (endothelial cells) and bottom channels (epithelial, smooth muscle cells, fibroblasts, pericytes) in contact through porous membrane.

13 Alexia Martin
alexia.martin18@imperial.ac.uk

4D live imaging for anti-mitotic chemotherapy predictive biomarker identification in 3D patient-derived organoid tumour models

Alexia Martin[1,2], Stephen Pettit[2], Chris Lord[2], Andrew Tutt[2,3] and Jorge Bernardino de la Serna[1]
[1] National Heart and Lung Institute; [2] The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research; [3] Breast Cancer Now Research Unit and School of Cancer and Pharmaceutical Sciences, King's College London

Standard-of-care therapy for many cancers, including lung and breast cancers, commonly involves treatment with anti-mitotic chemotherapies, primarily taxanes and vinca alkaloids. Unfortunately, there is a lack of biomarkers to predict tumour response to these agents, resulting in high occurrence of resistance and low efficacy in patients. Complex 3D patient-derived organoid (PDO) models are the optimal setting to identify novel biomarkers in vitro due to their clinically-relevant genetics and physiology. Current attempts in 2D cell line models cannot provide information on intra-tumour cell-cell interactions or the role of tumour heterogeneity in drug response. However, observing the drug mechanism of action – essential for identifying contributing factors to sensitivity or resistance – is yet to be achieved in 3D systems.

Our work aims to resolve anti-mitotic drug-driven mitotic arrest and related morphodynamic changes in 3D PDO tumour models through the development of live fast spatiotemporal high-resolution 4D imaging techniques. We have successfully multiplexed three independent biological markers (chromatin, tubulin, and plasma membrane integrity) and tracked their morphodynamic changes in up to 10 individual PDOs over 20 hours, enabling study of mitotic segregation errors induced under anti-mitotic drug exposure. We observe an average of 10 mitotic processes per organoid and have developed analysis pipelines to quantify mitotic arrest duration and mitotic segregation errors through the quantification of chromatin, microtubule and cell membrane morphodynamics. This enables comparison between the effects of different biological factors on anti-mitotic chemotherapy action.

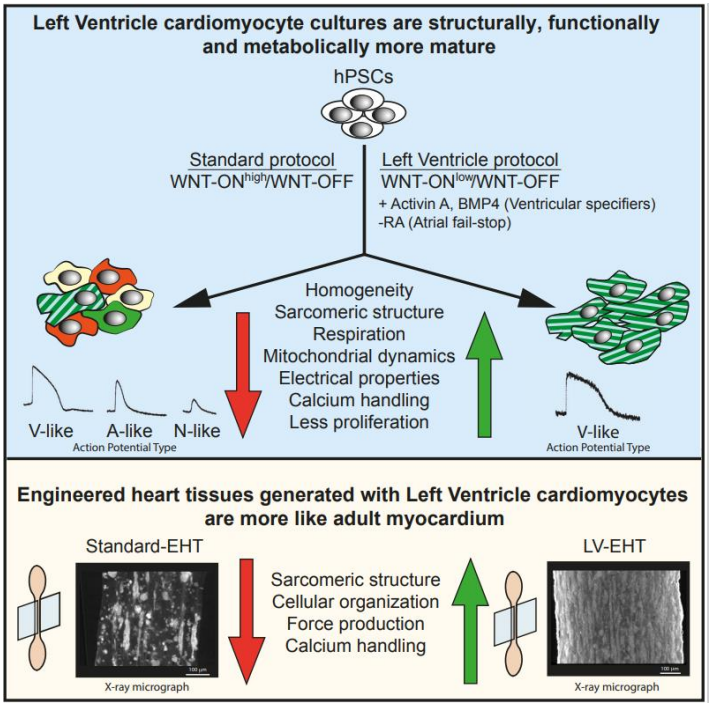
This work could identify novel biomarkers to inform clinical treatment strategies for anti-mitotic chemotherapies, thereby improving patient outcomes.

14 Andreia Sofia Bernardo
a.bernardo@imperial.ac.uk

Generation of left ventricle-like cardiomyocytes with improved structural, functional, and metabolic

Nicola Dark[2], Marie-Victoire Cosson[2], Lorenza I. Tsansizi[1,2], Thomas J. Owen[1], Elisa Ferraro[2], Alice J. Francis[1], Selina Tsai[2], Camille Bouissou[2], Anne Weston[2], Lucy Collinson[2], Najah Abi-Gerges[3], Paul E. Miller[3], Kenneth T. MacLeod[1], Elisabeth Ehler[4], Richard Mitter[2], Sian E. Harding[1], James C. Smith[2] and **Andreia S. Bernardo**[1,2]
[1] National Heart and Lung Institute; [2] The Francis Crick Institute, London; [3] AnaBios, San Diego, USA; [4] Kings College London

Decreased left ventricle (LV) function caused by genetic mutations or injury often leads to debilitating and fatal cardiovascular disease. LV cardiomyocytes are, therefore, a potentially valuable therapeutical target. Human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) are neither homogeneous nor functionally mature, which reduces their utility. Here, we exploit cardiac development knowledge to instruct differentiation of hPSCs specifically toward LV cardiomyocytes. Correct mesoderm patterning and retinoic acid pathway blocking are essential to generate near-homogenous LV-specific hPSC-CMs (hPSC-LV-CMs). These cells transit via first heart field progenitors and display typical ventricular action potentials. Importantly, hPSC-LV-CMs exhibit increased metabolism, reduced proliferation, and improved cytoarchitecture and functional maturity compared with age-matched cardiomyocytes generated using the standard WNT-ON/WNT-OFF protocol. Similarly, engineered heart tissues made from hPSC-LV-CMs are better organized, produce higher force, and beat more slowly but can be paced to physiological levels. Together, we show that functionally matured hPSC-LV-CMs can be obtained rapidly without exposure to current maturation regimes.



TOPIC 4	MECHANISMS UNDERLYING HEALTH AND DISEASE

ORAL PRESENTATIONS

Mascha Vinokurova
m.vinokurova21@imperial.ac.uk

Targeting the Rgl1 pathway to control vascular inflammation and atherogenesis

Mascha Vinokurova[1], Shih-Yu Lee[2], Hime Gashaw[1], Maria Lopes-Pires[1], Jane Mitchell[1] and Nicholas Kirkby[1]
[1] National Heart & Lung Institute; [2] Institute of Aerospace and Undersea Medicine, National Medical Defence Centre, Taiwan

Atherosclerosis and vascular inflammation are the underlying pathological mechanisms of coronary heart disease, which represents the number one cause of death worldwide. Current therapies focus on targeting lipids and platelets and treating risk factors. New clinical evidence suggests that targeting vascular inflammation may also be a viable approach to modify disease progression but to date there are no approved treatments for this for coronary heart disease patients. Here, we propose Rgl1, a mediator of the Ras/Ral pathway, as a novel regulator of vascular inflammation and potential therapeutic target. We have tested this using samples from heterozygous Rgl1-deficient mice. These mice showed no gross phenotypic changes and normal immune cell composition. Looking at atherogenic responses we found a reduction in LPS-induced adhesion molecule expression in Rgl1 deficient aortas. Moreover, reduced cytokine production without changes in oxLDL uptake, was observed in LPS-challenged Rgl1 deficient isolated peritoneal macrophages. In agreement, Rgl1 siRNA knock-down in LPS-challenged J774 macrophages reduced pro-inflammatory mediator release. Taken together this highlights the importance of Rgl1 in pro-inflammatory and atherogenic processes. Currently there are no compounds targeting

Rgl1 directly, but there are drugs in pre-clinical/clinical development targeting the Ras-/Ral-pathway upstream and downstream of Rgl1. Pharmacological inhibition of Ras, SOS1, SHP2 or Ral replicated the effect of Rgl1 deficiency in supressing LPS-induced inflammatory responses. These results will now be extended into in-vivo mouse atherosclerosis studies and patient samples to validate their potential to provide new therapeutic targets for vascular inflammation and identify compounds that can prevent and treat coronary heart diseases.

Amber Owen
a.owen19@imperial.ac.uk
Presence of neutrophils in the lungs prior to infection with RSV alters disease severity in mice

Amber Owen, Sophie Guan and Cecilia Johansson
National Heart & Lung Institute

The immune response to respiratory virus is thought to influence susceptibility to severe disease, but the exact determinants are unclear. Recently, in mouse models, recruitment of neutrophils prior to RSV infection by intranasal CXCL1, resulted in exacerbated weight loss driven by increased CD8+ T cell recruitment. As neutrophils are known to be short lived cells, we investigated how extending the time between neutrophil recruitment and RSV infection could alter disease outcomes.

Mice were intranasally pre-treated with CXCL1 12h or 48h prior to infection with RSV or X31. Weight loss was monitored, and the immune response was studied using flow cytometry, ELISA and qPCR.

Increasing the time between neutrophil recruitment and RSV infection to 48h, protected mice from RSV induced weight loss. Protection was associated with an increase in AMs (alveolar macrophages) in the lung and a trend to decreased proinflammatory cytokines at 18hpi. Overtime, neutrophils appeared to change phenotypically with increased expression of the maturation marker CD11b and Siglec-F. In addition, there was also an increase in percentage of neutrophils which were apoptotic. Apoptotic neutrophils in the lung are cleared by efferocytosis by AMs. We therefore co-cultured BAL cells harvested 6h or 48h after CXCL1, with murine BMDMs or mouse ex vivo AMs and subsequently infected with RSV. Co-cultures significantly altered the macrophage immune response to RSV, with 48h BAL cells driving a more anti-inflammatory response compared to 6h BAL cells. Overall, this suggests efferocytosis of dying neutrophils alters the AM response to RSV resulting in protection against disease.

Michael Lee
michael.lee@imperial.ac.uk
A cell and gene atlas of chronic ischaemic heart failure

Michael Lee[1], Lukas Mach[1,2], Kemar Brown[3,4], Eric Wei[3,4], Ursula Herbort-Brand[1], Anissa Viveros[5,6], Daniel M DeLaughter[3,4], Huachen Chen[5,6], Gavin Y Oudit[5,6], Jonathan G Seidman[3], Christine E Seidman[3,7,8], Sanjay K Prasad[1,2] and Michela Noseda[1,9]
[1] National Heart and Lung Institute; [2] Royal Brompton and Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust; [3] Department of Genetics, Harvard Medical School, USA; [4] Cardiac Unit, Massachusetts General Hospital, USA; [5] Division of Cardiology, Department of Medicine, University of Alberta, Canada; [6] Mazankowski Alberta Heart Institute, University of Alberta, Canada; [7] Cardiovascular Division, Brigham and Women's Hospital, USA; [8] Howard Hughes Medical Institute, USA; [9] British Heart Foundation Centre for Research Excellence and Centre for Regenerative Medicine, Imperial College London.

Heart failure (HF) due to ischaemic heart disease (IHD) is an important cause of early morbidity and death with an increasing number of patients affected. Although revascularisation therapies have significantly increased survival rates after an acute myocardial infarction, although mortality rates remain high (>35% at 5 years). Better understanding of mechanisms driving LV dysfunction in chronic IHD is required for defining novel therapeutic targets and improving outcomes. In this study, we performed single nuclei RNA-seq on cardiac tissue taken from patients with chronic IHD (n=24) and control donors (n=20) in order to elucidate the cellular and transcriptional drivers associated with maladaptive cardiac remodelling in ischemic HF. We identified changes in the cell type composition of the myocardium in IHD patients, with a decrease in cardiomyocytes and an increase in fibroblasts and endothelial cells compared to controls. All major cell types show changes in their transcriptional profile including the endocardial cells where we find upregulation of genes related to ECM organisation and collagen formation, suggesting that the endocardium plays a role in the fibrosis associated with IHD. These studies provide the opportunity to identify potential cellular and molecular targets for the treatment of the disease.

FLASH PRESENTATIONS

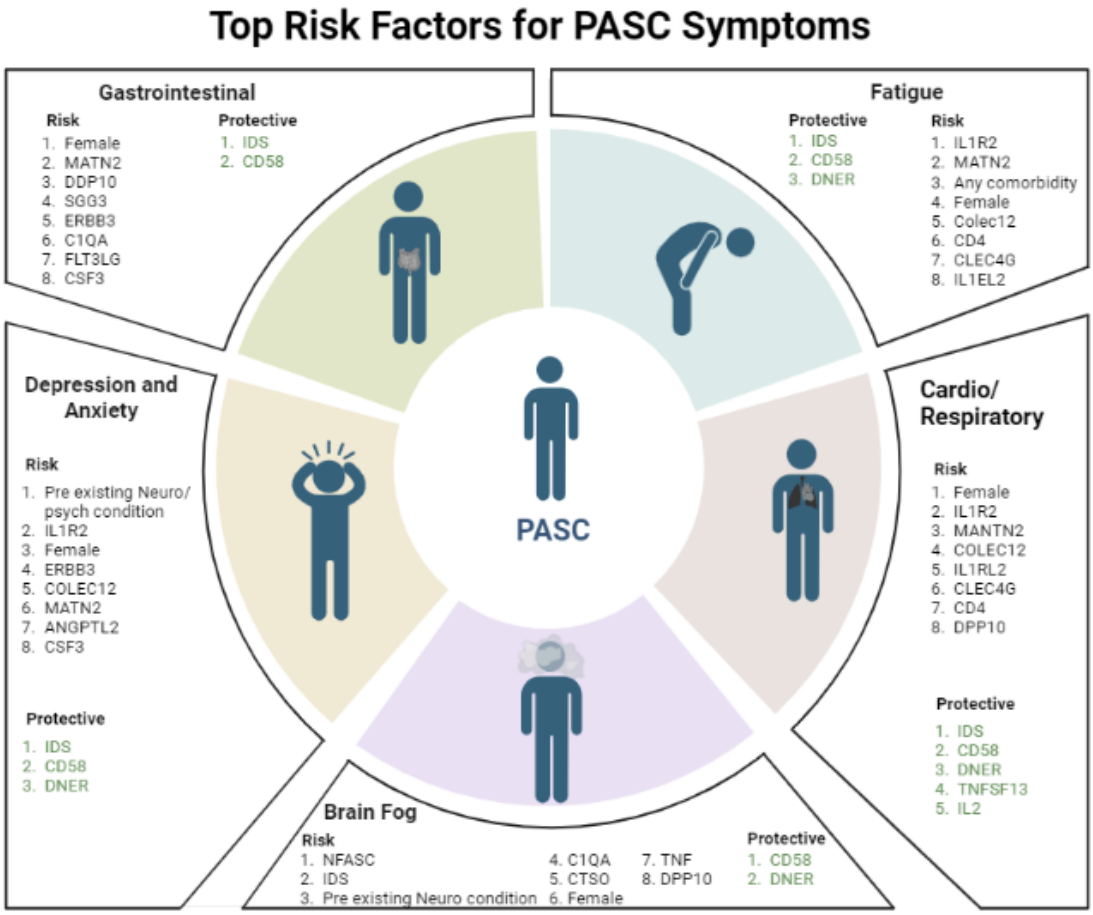
15 Claudia Efstathiou
c.efstathiou@imperial.ac.uk

Long Covid symptoms are driven by distinct proteomic profiles

Claudia Efstathiou, Felicity Liew, Ryan Thwaites and Peter J Openshaw
National Heart and Lung Institute

Introduction: Long COVID, or post-acute sequelae of COVID-19 (PASC), affects 30-60% of patients after SARS-CoV-2 infection. PASC is a heterogenous condition with a range of symptoms including shortness of breath, fatigue, and neurocognitive dysfunction. We hypothesised that each symptom group would have a distinct proteomic signature which could inform our understanding of the mechanisms of PASC.

Methods: The PHOSP consortium recruited over 7,000 hospitalised COVID-19 patients, a subset of whom were followed up at 5 and 12 months after discharge to provide blood samples and details of clinical status. Serum samples from 753 patients were analysed using the Olink proteomic Inflammatory panel to measure 368 proteins.



Result: Analysing symptom questionnaires, we identified 4 overlapping symptom group: Cardiopulmonary (72%), Fatigue (58%), Gastrointestinal (27%), Neuropsychiatric (53%), and Fully Recovered (20%). Analysing the symptom results with the proteomics through a penalized logistic regression showed that those reporting any PASC symptoms had high inflammatory markers compared to those who were fully recovered. Distinct protein signatures were associated with the different symptom groups, indicating different probable disease processes driving PASC. For example, neuropsychiatric symptoms were associated with elevated serum CCL20 (involved in chemotaxis of dendric cells), while gastrointestinal symptoms were associated with elevated CTRC (a marker linked to pancreatitis).

Conclusion: Regression modelling of a large dataset from UK patients with Long COVID indicates several symptom groups, each with its own serum proteomic profile. These novel findings suggest a physical basis for PASC, and that trials of therapy need to be adjusted to match these groups.

16 Qi Chen
qi.chen18@imperial.ac.uk

Investigating injury- and ageing-related alterations in lung tissue-derived extracellular vesicles and their effects on lung tissue

Qi Chen, Sally Yunsun Kim and Charlotte Dean
National Heart and Lung Institute

Introduction: Dysregulated lung regeneration is associated with ageing and underlies various lung diseases. Extracellular vesicles (EVs) contain bioactive molecules and mediate intrinsic lung regeneration, thus representing a promising therapeutic approach to lung diseases. While lung tissue-derived EVs likely contain intrinsic repair factors specific to lung repair, their therapeutic effects remain unexplored to date. This study investigated how injury- and ageing-associated physiological changes are reflected in composition of lung tissue-derived EVs and their ability to repair injured lung tissue.

Methods: EVs were derived from precision cut lung slices (PCLS) obtained from young (8-12 weeks-old) and aged (18 months-old) mouse lungs, with and without acid-induced injury. PCLS-EVs were characterised and their functional effects on post-injury lung repair were studied on PCLS with spatially restricted acid-induced injury (Kim et al., Biomaterials, 2021).

Results: Nanoscale flow cytometry revealed similar size or concentrations of EVs regardless of ageing or injury. Upon injury, both young and aged PCLS secreted EVs with apparently enriched RNA cargo. Injury increased type I collagen deposition in the extracellular matrix (9.25% to 35.83% in young and 24.07% to 37.33% in aged PCLS) and altered the actin cytoskeleton organisation in PCLS. A trend to decrease post-injury interstitial collagen accumulation (by 8.32%) was observed exclusively in young PCLS treated with EVs derived from young PCLS, while aged PCLS were unaffected by either EV treatment.

Discussion: The functional cargo of EVs is altered upon injury, and EVs derived from young lung tissue have pro-repair potential on lung injury, which should be investigated further.

17 Seran Hakki
s.hakki@imperial.ac.uk

Early rapid zinc metabolism has a role in determining optimal outcome post SARS-CoV-2 infection

Seran Hakki[1], Sean Nevin[1], Kieran Madon[1], Joe Fenn[1], Jakob Jonnerby[1], Emily Conibear[1], Aleksandra Koycheva[1], Robert Varro[1], Samuel Evetts[1], Rhia Kundu[1], Graham P Taylor[2] and Ajit Lalvani[1]
[1] NIHR Health Protection Research Unit in Respiratory Infections, National Heart and Lung Institute; [2] Department of Infectious Disease, Imperial College London

Zinc has an established role in the host defence against respiratory pathogens. We aimed to investigate the impact of early zinc metabolism on the outcome of SARS-CoV-2 infection.

We analysed blood samples from eighty-six SARS-CoV-2 infected patients collected within five days of symptom onset and measured their plasma zinc levels serially using mass spectrometry. Longitudinal RNA-sequencing and serum cytokine profiling was performed on a subset of cases. Symptom information was collected with daily questionnaires.

Zinc levels in cases were significantly raised on the first day of testing PCR-positive within the study (FP), and returned to baseline by FP+7-10 days (p=0.0001, n=59 pairs). At FP, lower zinc levels significantly associated with higher maximal measured viral load (VL) and viral AUC in cases (n=80), including after adjusting for age (p=0.011 and p=0.012). This relationship between zinc and viral outcome was also observed before cases tested PCR-positive (n=7), (p=0.039 and p=0.055). Asymptomatic cases (n=22) had higher zinc levels than symptomatic cases (n=59) (p=0.047). Cases with persistent cough, rhinitis, fatigue, and abdominal pain had lower zinc levels at FP than those without these symptoms (p=0.017, p=0.005, p=0.044, and p=0.046, respectively). Furthermore, our RNA-sequencing and serum cytokine profiling results provide insight into the mechanistic link between zinc and immune system modulation in response to SARS-CoV-2 infection.

These findings suggest that zinc is rapidly metabolised early during COVID-19 infection and may play a vital role in supporting immune function by activating the immune system while simultaneously regulating immunopathological inflammation.

18 Eleni Vasilaki
e.vasilaki@imperial.ac.uk
Use of multi-omics to uncover novel and druggable targets of SOX17 in PAH

Eleni Vasilaki[1], Rachel Walters[1], Yukyee Wu[1], Martin Wilkins[1], Inês Cebola[2] and Christopher Rhodes[1]
[1] National Heart and Lung Institute; [2] Department of Metabolism, Digestion & Reproduction, Imperial College London

Pulmonary arterial hypertension (PAH) is a complex and incurable disease, caused by the obstruction of the pulmonary vasculature, which leads to elevated mean pulmonary artery pressure and eventually right heart failure. This obstructive vascular remodelling is initiated by loss and then aberrant proliferation of pulmonary artery endothelial cells (PAEC) following injury. Endothelial transcription factor SOX17 plays a key role in vascular development and homeostasis and is a crucial genetic risk factor of PAH, with both rare and common genetic risk variants.

We hypothesize that SOX17 dysregulation leads to PAEC dysfunction, and this can be rescued by restoring SOX17 or its downstream targets. To achieve this, we performed epigenomic, transcriptomic and proteomic analyses to identify novel genes and pathways regulated by SOX17. Our results were passed into the LINCS drug:gene expression database to predict therapeutic compounds.

We have demonstrated that SOX17 loss alters PAEC proliferation, apoptosis and permeability. Additionally, based on PAEC-SOX17 ChIP-seq data annotation, 4605 genes have SOX17 binding at regulatory elements. Of these, there were 262 genes whose expression is affected by SOX17 manipulation and 9 genes whose levels in PAH patients' plasma are also associated with the SOX17 common disease risk variants, including EFNB2 and CTHRC1. We also identified 7 therapeutic compounds and showed that they reinstate HPAEC gene expression. Increased PAEC proliferation due to SOX17 loss was rescued by two compounds.

SOX17 dysregulation drives PAEC dysfunction, a key feature of PAH, and compounds that reinstate SOX17 physiological transcriptional signature may offer a strategy for rescuing this dysfunction.

19 Joy Nakawesi
j.nakawesi@imperial.ac.uk
The role of type I interferons in the generation of tissue-resident memory CD8+ T cell responses during RSV infection

Joy Nakawesi[1], Augusto Varese[2] and Cecilia Johansson[1]
[1] National Heart and Lung Institute; [2] Instituto de Investigaciones Biomédicas en Retrovirus y SIDA (INBIRS), Universidad de Buenos Aires, Argentina

The respiratory tract is the gateway for pathogens that represent threats to human health. Respiratory viruses, most commonly respiratory syncytial virus (RSV), constitute major burdens on healthcare systems. RSV causes severe lower respiratory tract infections, especially in children and the elderly. The lack of vaccines and recurrence of RSV infections indicate the difficulties in eliciting protective immune responses. Tissue-resident memory T cells (TRMs) are key players in memory responses at mucosal surfaces and play a central role in protecting from reinfection by respiratory viruses in mice and humans. In human experimental RSV infection, the presence of lung CD8+ TRMs correlates with a better outcome, however, the requirements for adequate lung TRMs responses during RSV reinfection are not fully understood. Type I IFNs are one of the early drivers of inflammation during viral infections and are critical anti-viral cytokines with pleiotropic effects. Type I IFNs are also important for T cell effector function, memory differentiation and survival.

We use mouse models to assess the role of type I IFNs in the generation and subsequent expansion of the TRMs pool during RSV infection.

We show that lung resident CD8+ TRM cells expand independently from systemic CD8+ T cells after RSV reinfection. Reinfected MAVS, MyD88/TRIF, and IFNAR1 deficient mice lacking key components involved in innate immune recognition of RSV and induction of type I IFNs, display impaired expansion of CD8+ TRM cells. IFN-α treatment of MAVS deficient mice during primary RSV infection restores the TRM cell expansion. Furthermore, bone-marrow chimeric mice show that the effect of type I IFNs on the generation of CD8+ TRMs is both via stromal and bone marrow-derived cells. Our data reveal how the axis controlling type I IFN induction instructs and regulates CD8+ TRM cell responses to RSV infection.

Reduced lab waste

Significantly less plastic as compared to leading supplier

Thinner-walled columns

Buffer bottles minimize plastic usage

Flexible purchasing options

Buffers and columns are sold separately

Same performance, design and formulations (same components as complete kits)

NEW ENGLAND BioLabs®

MONARCH® Sustainability

No excessive packaging

Sturdy, reusable boxes at just the right size

Concise protocol cards replace printed manuals

Sustainable & recyclable packaging

All components are purposefully sourced for recyclability

Instructions for recycling on packaging or online

Recycled paper (boxes, inserts and paper materials)

Eco-friendly printing (powered by green sources)

SARSTEDT

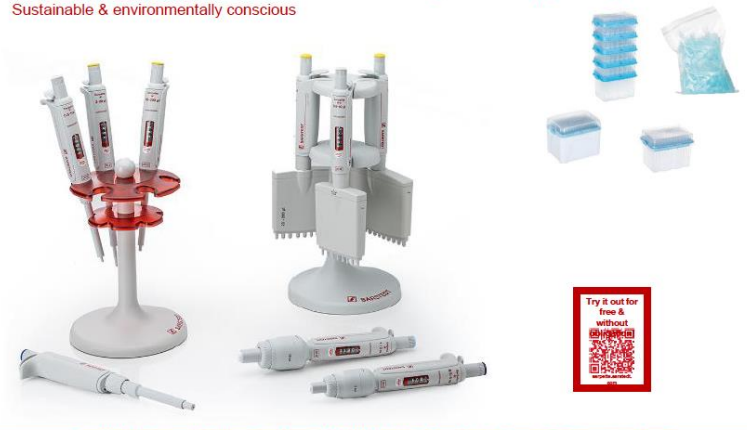
Mini Exhibition

Sarpette® M

One system – four options
Sustainable & environmentally conscious

Refill-Revolution

Systematic pipetting



Try it out for free & without

Sarstedt Ltd. • Optimus Way, Optimus Point Leicester LE3 8JR • Tel: 0116 235 9023 • info.gb@sarstedt.com • www.sarstedt.com

ThermoFisher SCIENTIFIC

COME AND MEET YOUR NEW THERMO FISHER ACCOUNT MANAGER!

Thermo Fisher Scientific Inc. is the world leader in serving science. Our Mission is to enable our customers to make the world healthier, cleaner and safer. Whether our customers are accelerating life sciences research, solving complex analytical challenges, increasing productivity in their laboratories, improving patient health through diagnostics or the development and manufacture of life-changing therapies, we are here to support them. Our global team delivers an unrivalled combination of innovative technologies, purchasing convenience and pharmaceutical services through our industry-leading brands, including Thermo Scientific, Applied Biosystems, Invitrogen, Fisher Scientific, Unity Lab Services, Patheon and PPD. Come speak to us to find out how we can help accelerate your research!

Karina Caetano Souza

Key Account Manager – Imperial College London, UK HSA & The Pirbright Institute

Mobile: +44 07824081075

Email: karina.caetanosouza@thermofisher.com