UNIVERSITY OF OXFORD

RADCLIFFE DEPARTMENT OF MEDICINE

RDM DAY 2026

Tuesday 17 March
8.45am-6.00pm

Mathematical Institute, Andrew Wiles Building

Come and celebrate our science and help build a culture in which all can thrive

Programme

8.45-9.10	**Registration, with tea and coffee available**
9.15-9.25	**Welcome and Introduction** (Lecture Theatre 1) Professor Keith Channon, Head of RDM
9.25-10.25	**Science Session 1: Metabolism and Molecular Medicine** (Lecture Theatre 1) *Chaired by Professor Hal Drakesmith* Svetlana Reilly: 'From cellular gene regulation to systemic metabolic signals in atrial fibrillation' James Grist: 'Magnetic resonance imaging: a window into metabolism' Daniela Nasteska: 'Dynamics of protein synthesis in pancreatic islets: new approaches and lessons learned'
10.25-11.05	**Coffee/Tea Break and Poster Sesion One** (Mezzanines)
11.10-12.10	**Science Session 2: Cell and Gene Therapy** (Lecture Theatre 1) *Chaired by Professor Steve Hyde* Deborah Gill: 'Gene therapy for rare lung disease: from model to medicine' Sumana Sharma: Optimising T cell manufacturing platform in RDM' Siyu Liu: 'Switching embryonic globin back on: a therapeutic genome editing strategy' Abhimanyu Gowda: 'The structural basis of MHC-II-restricted antigen recognition in the Graft-versus-Leukaemia effect'
12.10-13.40	**Lunch and Poster Session Two** (Mezzanines) **NB** If you would like to connect with clinician scientists over lunch, look out for the reserved table.
13.40-14.10	**Parallel Sessions** 1. **Grants: hints and tips** (L1), A panel chaired by Professor David Hodson, RDM 2. **Next steps with ChatGPT** (L2), Anders Reagan, University AI Compentency Centre 3. **Enabling career transition for professional services staff** (L3), Emma Engel and Manjiri Gokhale Joshi, RDM

14.15-15.15	**Science Session 3: AI and Medical Big Data** (Lecture Theatre 1) *Chaired by Professors Charalambos Antoniades and Qiang Zhang* Hashem Koohy: 'Decoding T cell recognition: opportunities and limits in the era of AI' Daniel Royston: 'From computational pathology to precision medicine in blood cancers: augmented spatial analysis of the bone marrow' Elizabeth Wahome: 'Predicting atrial fibrillation and stroke from CT images: the ORFAN Programme'
15.15-16.00	**Tea/Coffe Break and Poster Session Three** (Mezzanines)
16.05-16.15	**Graduate Prize Talk** (Lecture Theatre 1) 'Clearance or communication? Investigating how platelets shape the fate of extracellular DNA', Lauren Murphy
16.15-17.00	**Keynote Lecture** (Lecture Theatre 1) 'Obesity: causes, consequences and treatments', Professor Sadaf Farooqi, University of Cambridge
17.00-17.15	**Concluding remarks and prize giving** (Lecture Theatre 1)
17.15-18.00	**Drinks** (Mezzanine)

Calling all RDM Students: Look out for members of the RDM Student Forum who will be wearing purple lanyards and will be happy to chat with you!

How to connect to the Cloud WiFi

1. Select 'The Cloud' from the available WiFi networks on your mobile device. This should prompt a landing page with a button to log-in or register.
2. If the landing page doesn't open automatically, open your browser. If it still won't load, type bbc.co.uk to prompt the browser to load the landing page.
3. If it is your first time using The Cloud WiFi, you will need to create your own personal log-in. Select 'register' and follow the one-time registration process.
4. Once registered you can access the internet via The Cloud. Save or remember your log-in details for future use.

Posters

No	Name	Poster Title
1	Megan Payne	'Bug-To-Drug: Scaffold-imposed pharmacophore geometry enables selective control of immune cell migration'
2	Medina Abudula	'Molecular mechanisms of cholangiocyte–cholangiocarcinoma crosstalk in early cholangiocarcinoma'
3	Galina Boskh	'Integrative omics approach to uncover limiting mechanisms that regulate lentiviral vector transduction in hepatocytes'
4	Karmella Naidoo	'The role of CD1a in sensing stress changes and barrier disruption in the skin'
5	Marco Muccio	'Optimising MRI acquisition for spinal cord imaging'
6	Casey Johnson	'Guideline discordance in real-world human reporting of left ventricular diastolic function'
7	Dagmara Korona	'Using iPSC and mouse models to investigate causality of structural variants in craniofacial disorders'
8	Siyu Chen	'Cell-intrinsic and systemically aligned circadian clocks are essential for Kupffer cells to maintain cellular function and liver homeostasis'
9	Waleed Seddiq	'Hypertrophic cardiomyopathy modulates extracellular vesicles release and composition to promote inflammation, extracellular remodelling and fibrotic signalling'
10	Marta Moya Jodar	'Functional analysis reveals the unique cellular mechanisms of Friedreich's Ataxia cardiomyopathy'
11	Wei-Che Chang	'ICOS defines recent thymic emigrant T Cells with distinct functional properties'
12	Chenham Sam Ma	'Investigating the role of Interleukin-11 (IL11) with Interleukin-6 (IL6) in atrial fibrillation'
13	Shuchishmita Maitra	'In vitro evaluation of novel antifibrotic compounds in human atrial fibroblasts'
14	Daniel Rosoff	'Genetic co-localisation identifies shared genetic architecture for sleep/circadian traits, and prevalent cardiometabolic disease'

15	Jason Chai	'Association of inflammation and extent of coronary artery disease in type 2 diabetes (T2D) and acute coronary syndrome (ACS)'
16	Charlotte Hooper	'Generation of VCAM-1 expressing bioengineered extracellular vesicles for immune cell targeting'
17	Michail Mavrogiannis	'Novel AI biomarker of metabolically unhealthy adipose tissue predicts cardiometabolic risk in patients undergoing CCTA'
18	Anna-Sophie Haselon	'Epigenetic editing of therapeutic T cells'
19	Stephanie Anderson	'Plasma extracellular vesicles in people with diabetes following acute myocardial infarction'
20	Katherin Boden	'Re-distribution of histone H4 lysine 16 acetylation in macrophages following pro-inflammatory activation'
21	Kenneth Chan	'The interplay of systemic and local coronary inflammation in cardiovascular risk prediction'
22	Shahzaib Tariq	'Human endogenous lentiviral particles (HELP) for the delivery of CRISPR ribonucleoprotein complexes'
23	Lei Deng	'Gastric epithelial remodelling as an early defence against helicobacter pylori'
24	Anna Sozanska	'Automated IHC detection and spatial statistical analysis for validation of spatial transcriptomic experiments'
25	Dimitrios Ioannidis	'Visualising tight junction formation in developing human gut with STED super-resolution microscopy'
26	Kexin Xu	'Predicting spatial transcriptomics from histology images of inflammatory bowel disease'
27	Garvin Turnbull	'High-efficiency in vivo genome editing of SERPINA1 using homology-independent targeted integration (HITI)'
28	Arlene Glasgow	'Using induced pluripotent stem cells (iPSC) to develop a model for ABCA3 surfactant deficiency'
29	Daniel Foran	'Natriuretic peptides reverse vascular endothelial insulin resistance and ameliorate dysregulated redox signalling when administered alongside insulin in human atherosclerosis'

30	Giulia Pironaci	'Iron deprivation impairs human B cell activation, proliferation and differentiation in vitro'
31	Hannah Murray	'Cellular iron deficiency impairs mast cell development and degranulation'
32	Toby Whitehead	'Studying the function and expression of TIM-3 on cytotoxic T cells'
33	Yang Hu	'Exploring the role of Arsenite-3-Methyl Transferase (As3mt) in cardiometabolic disease'
34	James Garrard	'Stroke-specific early warning score improves the prediction of deterioration for stroke patients in hospital: a retrospective cohort study'
35	Josephine Sandercock	'Statistical methods for split-sample laboratory studies: observations from a systematic review of irradiated platelets'
36	Rosemary Kirk	'Divergent functional consequences of different TTN truncating variants in dilated cardiomyopathy'
37	Sarah Armour	'The synaptic glycoprotein CBLN4 acts as a paracrine messenger controlling insulin and glucagon secretion in pancreatic islets'
38	Christopher Carlein and Imogen Rayer	'Characterising GLP1R/GLP1R expression in human iPSC-derived pancreatic islets (SC-islets) for cell therapy applications'
39	Jackson White	'ITGBP4 at the nexus between mechanotransduction and post-transcriptional regulation'
40	Catherine Kimber	'Assessing risk of bias for in vitro studies of split (paired) samples included in a systematic review of irradiated platelets'
41	Carolyn Dorée	'Does irradiation affect the quality, effectiveness, and safety of platelets for transfusion? A systematic review'
42	Jhiamluka Solano Velasquez	'Developing an integrated cardiac magnetic resonance and cardiopulmonary exercise testing platform to characterise exercise intolerance'
43	Shakila Bibi	'Analysing hypertensive multi-organ damage across different ethnic groups in the UK Biobank'

Information stands to browse during breaks

RDM EDI and Mentoring: Come and meet RDM's EDI Facilitator, EDI Champions, and Mentoring Coordinator. Contribute your ideas for how to foster an inclusive culture.

The RDM Researcher Association & RDM Student Forum: These two groups build community in RDM by bringing researchers and students together with their peers across the department.

Oxford University Innovation: OUI provides academics, staff and students with advice and support on the commercialisation of research and expertise.

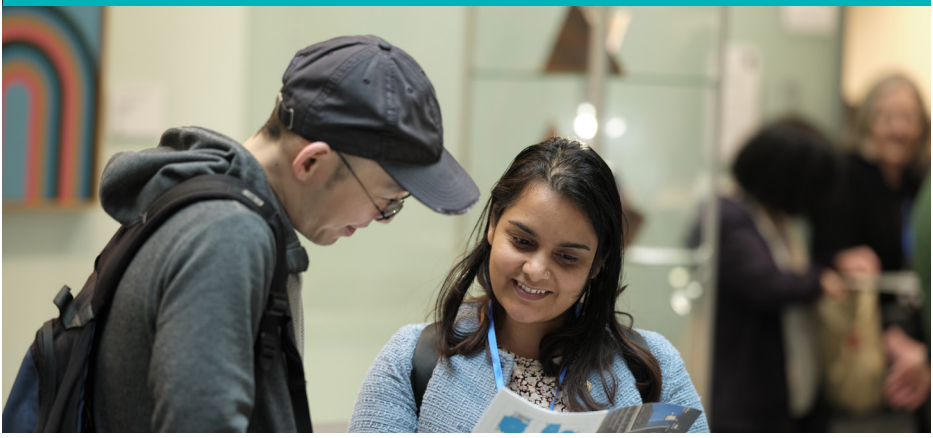
Environmentally Sustainable Research: Come and talk to people from across RDM who are championing environmental sustainability in different areas of our department.

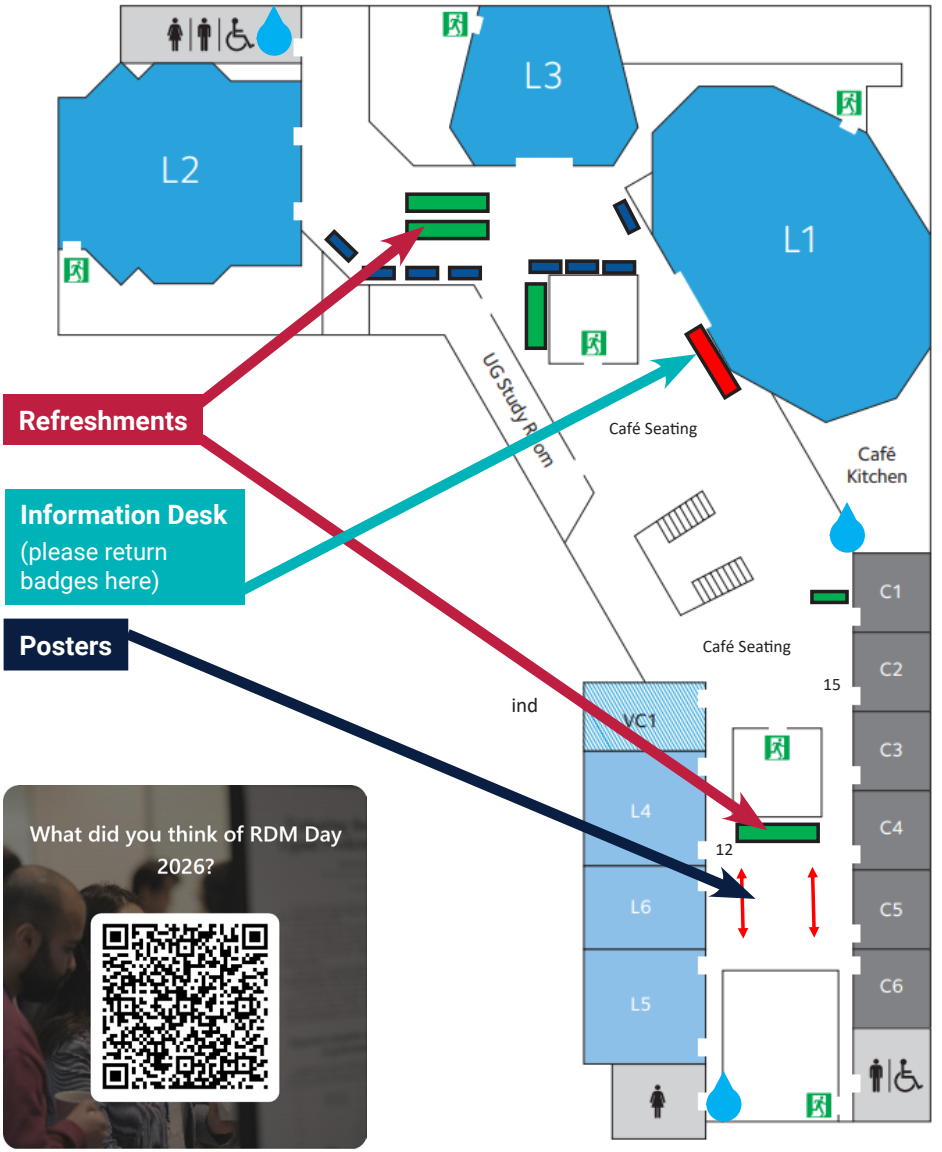
AI Competency Centre: The AI Competency Centre offers resources and training to ensure that everyone can use AI tools with confidence and safety.

Open Scholarship: Discover resources relating to open access, research data management, copyright and licensing and digital preservation.

People and Organisational Development: Find out about staff development opportunities, from management and leadership programmes to mentoring and coaching schemes.

Translational Research Office: Meet this team who can help reseachers translate findings from basic research into practical human health benefits.





NB If you require a quiet place to pray during Ramadan, please ask at the main Maths reception.

Download a virtual version of this programme including links to speaker profile pages and full abstracts of all posters.

Poster number: 1

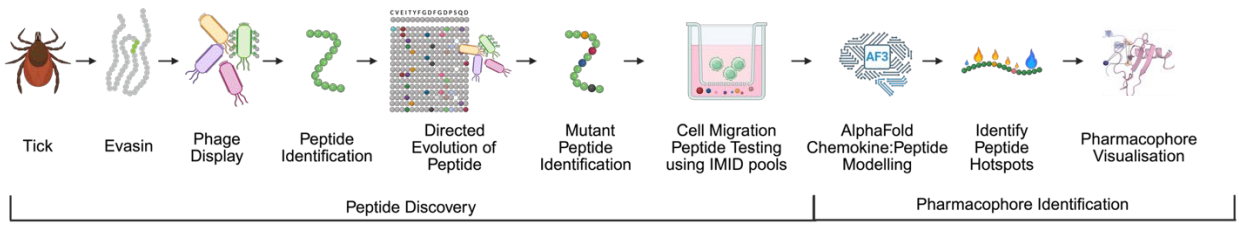
Bug-To-Drug: Scaffold-imposed pharmacophore geometry enables selective control of immune cell migration

Megan Payne*, Fernando Duraes, Charlie J. Clark, Emma Wilde, Kalimuthu Karuppanan, Soumyanetra Chandra, Gintare Smagurauskaite, & Shoumo Bhattacharya

Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, UK.

*Megan Payne is the presenting author and is a postdoctoral researcher.

Immune-mediated inflammatory diseases (IMIDs) are sustained by the chemokine-driven recruitment of effector T-cells into tissues. While therapies that suppress T-cell function can be effective, their use is limited by the systemic immunosuppression they induce. Targeting chemokine networks offers an alternative strategy, but functional redundancy within these systems has hindered therapeutic development. Tick salivary evasins overcome this challenge by binding multiple chemokines and blocking receptor engagement, although their size and complexity limit clinical translation. Here, we describe the directed evolution of a class B evasin-derived peptide that selectively inhibits T-cell, but not monocyte, migration in response to individual chemokines and IMID-mimicking chemokine pools. This contrasts with previously described class A evasin-derived peptides, which broadly inhibit migration of multiple immune cell types. Structural and interface analyses support steric occlusion of chemokine receptor-binding surfaces as a shared mechanism of inhibition. Pharmacophore modelling reveals that, despite conserved chemokine-binding chemistry comprising ionisable and hydrophobic features, class A and class B peptides adopt distinct scaffold-imposed geometries. Class A-derived peptides exhibit a more extended ionic–hydrophobic arrangement, whereas class B-derived peptides form a compact interaction patch. These geometric differences provide a plausible explanation for their divergent functional profiles. Together, these findings identify class B evasin-derived peptides as promising starting points for the development of selective therapeutics that modulate chemokine-driven T-cell migration while sparing other immune cell populations in IMIDs. Ongoing efforts focus on improving peptide potency and stability, and tissue-targeted delivery to minimize systemic immunosuppression.



Poster number: 2

Title: Molecular mechanisms of cholangiocyte–cholangiocarcinoma crosstalk in early cholangiocarcinoma

Medina Abudula (Postdoc), Gemma Owen, David Kerr, Shijie Cai

Nuffield division of clinical laboratory sciences, RDM, Medical Science Division

Abstract

Cholangiocarcinoma (CCA) is a highly aggressive malignancy of the bile ducts, characterized by poor survival rates and limited treatment options. The tumour microenvironment, including the fibroblasts, endothelial cells and immune cells, in known to support CCA progression, yet the role of the cells from which CCA originates, the biliary epithelial cells (cholangiocytes), remains underexplored. Here, we investigate the early crosstalk between cholangiocytes and cholangiocarcinoma cells and its impact on tumour initiation and progression.

In this study, we employed an indirect co-culture system combined with metabolomic, transcriptomic and secrotome analysis to dissect this interaction. Indirect co-culture of CCA cells with cholangiocytes led to increased CCA cell apoptosis, reduced invasive capacity and alterations in epithelial-mesenchymal transition (EMT)-related protein expression consistent with a hybrid EMT state. Co-culture also induced a metabolic reprogramming in CCA cells, including altered branched chain amino acid (BCAA) metabolism, and a transcriptomic shift towards enhanced cytokine, which was mirrored in the secretome profile. Conversely, cholangiocytes exposed to CCA cells exhibited a persistent growth advantage, high inflammatory cytokine production, and increased creatine metabolism and ATP availability, associated with improved viability and reduced apoptosis.

These findings suggest that even before the full malignant transformation, bidirectional signalling between cholangiocytes and CCA cells modulates survival, inflammation and metabolic adaptation, thereby priming the microenvironment for CCA progression. Overall, this work highlights cholangiocyte as active modulators of early cholangiocarcinoma development (Figure.1).

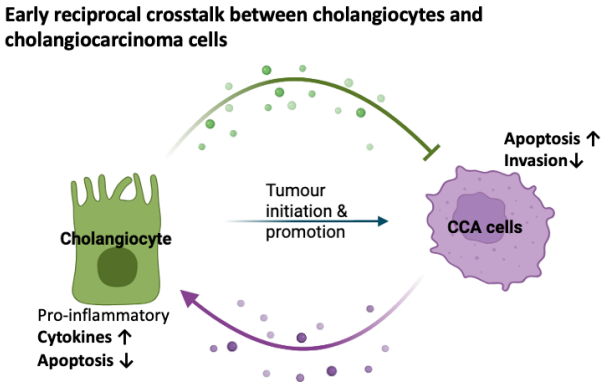


Figure 1. Graphical abstract illustrating reciprocal signalling between cholangiocytes and CCA cells, showing altered apoptosis, invasion and pro-inflammatory cytokine production in both cell types

Poster number: 3

Integrative omics approach to uncover limiting mechanisms that regulate lentiviral vector transduction in hepatocytes

Authors: Galina Boskh[1] (PhD student), Kshitiz Tyagi [2], Shaan Subramaniam[2], André Raposo [2,] Stephen Hyde[1] , Shijie Cai[1]

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Introduction

The liver is a key target for gene therapy due to its central role in metabolism and protein secretion. However, efficient transduction of quiescent adult hepatocytes with lentiviral vectors (LVs) remains challenging, possibly due to intracellular factors limiting LV entry, integration, and transgene expression. We aim to investigate metabolic pathways to optimise the cellular environment and to enhance LV transduction in hepatocytes.

Methods

Transduction efficiencies of VSV-G pseudotyped, EGFP-expressing HIV- and SIV-derived LVs were compared in THLE-2 normal hepatocytes, HepG2 hepatocellular carcinoma cells, and HEK293T cells. Proliferation, LV receptor (LDLR) abundance, and vector integration (VCN), were assessed using IncuCyte, immunoblotting, qPCR, and ddPCR (assay precision ~2-fold). Chromatin regulation was examined using epigenetic chemical probes. Proteomics and metabolomics were performed on FACS-sorted transduced and non-transduced cells, followed by integrated multi-omics analysis.

Results

LV transduction did not affect cell viability or proliferation. HIV-LV achieved ~2-fold higher transduction efficiency than SIV-LV across all cell lines and ~2-fold higher VCN in HepG2 cells. Transduction efficiency of THLE-2 cells was ~3-fold lower than in HepG2 and HEK293T, regardless of vector, correlating with reduced LDLR expression. Inhibition of histone lysine methyltransferases reduced HIV-LV transduction, implicating a regulatory role for chromatin state. Proteomics analysis revealed enrichment of metabolic, cell cycle, and chromatin regulatory pathways in transduced cells, while metabolomics identified increased abundance of pentose phosphate pathway, amino acid and TCA cycle metabolites in these cells, linking metabolic state to LV permissivity.

Conclusion

Reduced LV transduction in THLE-2 cells and metabolic pathway enrichment in successfully transduced cells suggest a potential role for intracellular metabolic state in LV permissivity, currently under investigation using multi-omics analysis.

Poster number: 4

The role of CD1a in sensing stress changes & barrier disruption in the skin

Karmella Naidoo[1,2], Wojciech Lason[3], Clare Hardman[1], Uzi Gileadi[1,] Tan-Yun Cheng[4] Paola Vargas Gutierrez[5], Rosana Ottakandathil Babu[1], Adrian Kobiela[1], Jessica Soo Weei Ng[1], Laura Ciacchi[1], Aaron Moore[1], Maria Greco[5], Yi-Ling Chen[1,2], Calliope Dendrou[3], Gurdyal Besra[6], Jamie Rossjohn[7], Branch Moody[4] and Graham Ogg[1,2]

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[7]Infection and Immunity Program and Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute Monash University, Clayton, Victoria, Australia.

Background: Cluster of differentiation 1a (CD1a) is highly expressed on Langerhans cells (LCs) and has been increasingly implicated in the pathogenesis of skin diseases such as atopic dermatitis (AD). Studies have shown that the CD1a pathway can be inhibited by very long chain sphingomyelins. We aimed to determine the role of CD1a in sensing stress changes in the skin as well as the efficacy of synthetic sphingomyelin analogues.

Methods: We used a murine model of MC903 application, that induces an early type two phenotype, similar to the AD phenotype observed in patients. MC903 was topically applied to the skin of humanised CD1a transgenic mice (CD1atg) and controls, in the presence or absence of CD1a blockers. We assessed the role of pruritus and mediators of itch TSLP and IL-33. Skin thickness, scratching behaviour, immune cell infiltration and tissue chemokine levels were evaluated. In addition, we explored key cell niches through the use of spatial transcriptomics.

Results: The findings demonstrated a profound skin alarmin signature, increased skin inflammation, itching and immune dysregulation, in the setting of CD1a.The sphingomyelin analogues strongly inhibited MC903-induced pruritus and led to significant reduction in inflammatory parameters. Furthermore, spatial transcriptomic analysis revealed nodal mechanistic insights into CD1a pathway inhibition.

Conclusion: The amplified dermatitis-like phenotype induced by MC903 in CD1atg suggests an unexpected role for CD1a in the induction of pruritus, partly mediated by TSLP. Additionally, the data suggest a role for synthetic sphingomyelin CD1a blockers as a therapeutic option in the treatment of AD.

Poster number: 5

Optimizing MRI Acquisition for Spinal Cord Imaging

Marco Muccio[1†], Damian Tyler[1], James T Grist[1]

[†]DPhil student

[1]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, Oxford Center for Magnetic Resonance Research, University of Oxford, Oxford UK

Abstract

Spinal cord MRI is central to diagnosing and monitoring of several neurological diseases and injuries, yet it remains technically challenging because of the cord's small size, heterogeneous surroundings, and sensitivity to respiratory, vascular, and cerebrospinal fluid motion. The spinal cord is particularly relevant in multiple sclerosis (MS), where recent diagnostic criteria incorporate spinal lesions which correlate strongly with disability and prognosis[1,2]. Nevertheless, spinal MRI remains comparatively underdeveloped relative to brain imaging.

This study aimed to optimize MRI sequences sensitive to MS pathophysiology to inform improvements in clinical spinal protocols. Five healthy volunteers (mean age ~25 years; three males) were scanned on a 3 T GE system using head and chest coils. Acquisitions included routine contrasts (T1-weighted, T2-weighted, proton density) and advanced techniques such as T2* mapping, white-matter-null, magnetization transfer ratio, and diffusion tensor imaging.

Optimization focused on improving resolution, signal-to-noise ratio, and robustness to motion. Dynamic local shimming and saturation bands around the field of view consistently improved image quality across sequences. Dividing acquisitions into two cervical blocks enabled better compensation for spinal curvature and more accurate axial orientation. For motion-sensitive sequences, PROPELLER approaches minimized motion effects, while cardiac-triggered (ECG and pulsoxymeter) T2* mapping minimized pulsatility artifacts (ghosting in phase encoding direction) by synchronizing acquisition to the cardiac cycle.

Ongoing work will assess repeatability, compare reconstruction strategies, and refine a clinically-feasible comprehensive spinal MRI protocol to be investigated in MS patients, with the goal of enabling earlier diagnosis, differential diagnosis, treatment monitoring, and ultimately improve patient care.

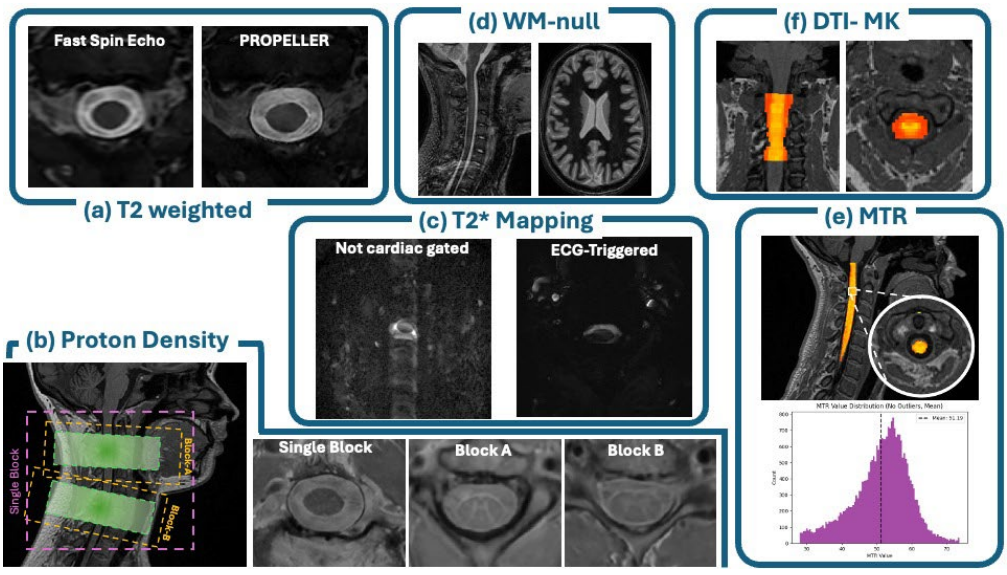

Figure 1. Representation of the main MRI sequences investigated here. **(a)** T2-Weighted images showing improved resolution with PROPELLER compared to cartesian fast spin echo. **(b)** Proton density sequence showing the improved spatial resolution by dividing acquisition into two blocks (yellow) compared to a single block (violet). **(c)** T2* weighted images in which pulsation artifacts are corrected by applying cardiac gated acquisition (ECG). **(d)** White matter null (WM-null) images highlighting the suppression of MR signal from the white matter in healthy brain and spine. **(e)** Magnetization transfer ratio (MTR) sequence with regions of interest in the cervical spine reporting expected MTR value distributions. **(f)** Diffusion tensor images of voxel-wise mean kurtosis being greater in the spinal cord compared to surrounding CSF, as expected.

References:

1) Montalban X, Lebrun-Frénay C, Oh J, Arrambide G, Moccia M, Pia Amato M, Amezcua L, Banwell B, Bar-Or A, Barkhof F, Butzkueven H, Ciccarelli O, Chataway J, Cohen JA, Comi G, Correale J, Deisenhammer F, Filippi M, Fiol J, Freedman MS, Fujihara K, Granziera C, Green AJ, Hartung HP, Hellwig K, Kappos L, Kimbrough D, Killestein J, Lublin F, Marignier R, Ann Marrie R, Miller A, Otero-Romero S, Ontaneda D, Ramanathan S, Reich D, Rocca MA, Rovira À, Saidha S, Salter A, Sastre-Garriga J, Saylor D, Solomon AJ, Sormani MP, Stankoff B, Tintore M, Tremlett H, Van der Walt A, Viswanathan S, Wiendl H, Wildemann B, Yamout B, Zaratin P, Calabresi PA, Coetzee T, Thompson AJ. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. Lancet Neurol. 2025 Oct;24(10):850-865. doi: 10.1016/S1474-4422(25)00270-4. Erratum in: Lancet Neurol. 2025 Nov;24(11):e13. doi: 10.1016/S1474-4422(25)00355-2. PMID: 40975101.
2) Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, Rovira A, Sastre-Garriga J, Tintorè M, Frederiksen JL, Gasperini C, Palace J, Reich DS, Banwell B, Montalban X, Barkhof F; MAGNIMS Study Group. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol. 2016 Mar;15(3):292-303. doi: 10.1016/S1474-4422(15)00393-2. Epub 2016 Jan 26. PMID: 26822746; PMCID: PMC4760851.

Poster number: 6

Guideline Discordance in Real-World Human Reporting of Left Ventricular Diastolic Function

Casey L Johnson[1*], Andrew Fletcher[1], Samuel Krasner[1], , Sadie Bennett[1], Michael Johnston[2], , Ross Upton[3], Amanda Adler[4], Paul Leeson[1]
*Presenting author is a DPhil student
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[3]Ultromics LTD., United Kingdom
[4]Oxford Centre for Diabetes, Endocrinology, and Metabolism, Radcliffe Department of Medicine, University of Oxford, United Kingdom

Introduction
Echocardiography is widely used to assess left ventricular diastolic function, but guideline-directed assessment is complex [1–4]. We evaluated how diastolic function is reported in routine practice across NHS district general hospitals and tertiary centres and compared real-world reporting with guideline-directed assessments generated by a fully automated tool based on international guidelines, to identify gaps in current practice.
Methods
Anonymised echocardiography data were extracted from hospitals within a large academic NHS Trust via the EchoVision observational study (19/HRA/2068), with additional manual extraction from five independent NHS Trusts across England through the ECHO-AID study (25/HRA/1405) to ensure generalisability. Operator-reported diastolic function was extracted using bespoke keyword-search algorithms in R. American and British Society of Echocardiography guidelines were implemented in an automated pipeline and validated against expert consensus. Operator-reported and automated assessments were compared, and temporal trends analysed using linear regression.
Results
A total of 150,574 echocardiograms performed between 2017 and 2025 were analysed. Diastolic function was reported in 96,916 studies (64.4%). Of these, 84,889 (87.6%) used detailed categorisation, while 12,027 (12.4%) referred to impaired diastolic function or elevated filling pressures without further detail. The automated pipeline categorised diastolic function in 100% of studies, although 51% were unclassifiable under guideline criteria due to missing data or confounders. Concordance between operator and automated categorisation increased significantly over time (β = 1.33 percentage points/year, p = 0.027), representing a 10.6% increase since 2015 (Figure 1).
Conclusions
Over a quarter of echocardiograms lacked diastolic function reporting, consistently across hospitals. Automated assessment revealed important discrepancies with human reporting, although agreement has improved over time. Further evaluation is needed to determine whether automated tools can improve consistency, speed, and accuracy of reporting.

References

1. Nagueh, S. F. *et al.* Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography and for Heart Failure With Preserved Ejection Fraction Diagnosis: An Update From the American Society of Echocardiography. *Journal of the American Society of Echocardiography* **38**, 537–569 (2025).
2. Robinson, S. *et al.* The assessment of left ventricular diastolic function: guidance and recommendations from the British Society of Echocardiography. *Echo Res Pract* **11**, 16 (2024).
3. Mathew, T. *et al. A Guideline Protocol for the Echocardiographic Assessment of Diastolic Dysfunction*. https://www.bsecho.org/common/Uploaded%20files/Education/Protocols%20and%20guidelines/Diastolic%20dysfunction.pdf (2013).
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Poster number: 7

Using iPSC and mouse models to investigate causality of structural variants in craniofacial disorders

Dagmara Korona[1], Akiko Soneda Hashimoto[1*], Yang Pei[1*], Eduardo Calpena[1,2], Jackie Sloane-Stanley[3], Simone G Riva[3], Ron Schwessinger[3], Siddharth Banka[4,5], Satyan Chintawar[6], Galbha Duggal[6], Francesca Forzano[7], Astrid Weber[8], Steven A Wall[9], Jim R Hughes[3], Stephen R F Twigg[1,10,†], Andrew O M Wilkie[1,9,10,†]

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*These authors contributed jointly to this work

†These authors co-supervised the work

Background: Unravelling the causal links between unique structural/copy-number variants (SV/CNV) and craniofacial disorders is challenging, but essential for correct genetic counselling. The organisation of the 3D genome into regulatory units termed topologically-associating domains (TADs), provides a useful framework to explore pathogenic mechanisms of SV/CNV. We evaluated the application of patient-derived induced pluripotent stem cells (iPSCs) differentiated to relevant cell types as an alternative to construction of mouse models for experimental testing of causal hypotheses.

Subjects: We investigated four unrelated families in which patients with craniofacial disorders harboured unique chromosomal duplications (dup) that either (i) potentially dysregulated specific FGF-encoding genes (*FGF5* [730 kb dup] or *FGF9* [568 kb interspersed dup]) or (ii) had duplications involving the *HOXC* cluster, whereby individuals with a smaller (286 kb) dup paradoxically manifested a more severe phenotype than those with a larger (941 kb) dup that completely encompassed the smaller one.

Methods: We used deepC to predict the consequence of each duplication on local TAD organisation. iPSCs were derived from an affected family member and differentiated to neural crest cells. For cases potentially involving FGFs we further differentiated the cells to osteogenic progenitors. Where feasible (2 cases) we generated a mouse bearing an equivalent rearrangement using CRISPR-Cas9 targeting. Effects on gene expression and chromatin accessibility were analysed using RNA and ATAC sequencing, respectively.

Results: In three cases (both those involving an FGF-encoding gene, and the smaller *HOXC* dup) deepC predicted the generation of a neo-TAD, potentially leading to misregulated expression of a key developmental FGF/HOXC-encoding gene; by contrast the 941 kb dup was predicted to duplicate the entire *HOXC*-associated TAD, without altering local gene regulation. Each prior hypothesis was supported by RNA sequencing, which demonstrated significant and specific upregulation of the predicted gene (*FGF5*, *FGF9*, or *HOXC10*), which was further confirmed by quantitative reverse transcriptase PCR. Corresponding changes in chromatin accessibility were observed in the ATAC-sequencing data.

Conclusion: To our knowledge this is the first time that a differentiated iPSC-based approach has been applied to the pathological investigation of SV/CNV in patients with craniosynostosis. Our results show striking concordance with predictions of altered TAD structure from deepC modelling, supporting that for this application, the iPSC-based methodology may provide a realistic alternative to the laborious construction of mouse models.

Poster number: 8

Title: Cell-intrinsic and systemically aligned circadian clocks are essential for Kupffer cells to maintain cellular function and liver homeostasis

Authors: Siyu Chen[1, 2] (DPhil student), Noelia Martinez-Sanchez[1, 2], Hua Pu[3], Nicola Smyllie[4], Michael Hastings[4], David Ray[1, 2]

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Abstract:
Macrophages are key components of the innate immune system with remarkable tissue heterogeneity[1]. Kupffer cells (KCs), the liver-resident macrophages, orchestrate immune, and metabolic functions to maintain hepatic homeostasis[2]. The circadian system is essential to macrophage function, but its role in KC is completely unexplored[3]. Using PER2::luc transgenic mice, we demonstrated that KCs possess intrinsic circadian clocks capable of sustaining rhythmicity *ex vivo* under constant conditions. We then investigated the functional importance of this intrinsic clock by targeting *Bmal1*, the only non-redundant circadian clock gene. Genetically, myeloid-specific deletion of *Bmal1* markedly altered KC morphology by reducing adherence and disrupting actin organisation. Pharmacologically, similar phenotypes were induced by a novel small-molecule BMAL1 ligand Core Circadian Modulator (CCM)[4]. Our recent data showed that CCM reversibly inhibits transactivation of the BMAL1:CLOCK heterodimer as well as amplitude of oscillation in the suprachiasmatic nucleus, revealing exciting potentials for selective clock targeting. We then examined the impact of circadian disturbance on KCs and liver physiology in a disease context. Metabolic dysfunction-associated steatohepatitis (MASH) is an increasing global health concern closely connected to sleep and circadian disruption[5]. We induced MASH in mice using a choline-deficient, L-amino acid-defined high-fat diet (CDA-HFD) combined with either chronic jetlag (CJ) or a standard 12:12 light-dark cycle. We showed that CJ significantly exacerbated MASH pathology. Single-nucleus RNA sequencing further identified hepatocytes and hepatic macrophages as the most affected cell types. In macrophages, altered expression of *Fkbp5*, *Tlr7*, and *Vcam1* points to dysregulated glucocorticoid response, pro-inflammatory and monocyte infiltration processes as potential key mechanisms linking CJ to exacerbated MASH. Together, these findings demonstrate that KC function and liver homeostasis critically depend on intact, cell-intrinsic circadian clocks aligned with systemic rhythms.

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Poster number: 9

Title: Hypertrophic cardiomyopathy modulates extracellular vesicles release and composition to promote inflammation, extracellular remodelling and fibrotic signalling.

Authors: Waleed Seddiq[1,2*], Yiangos Psaras[1], Jonathan Chan[1], Anuj Goel[1], Hugh Watkins[1], Christopher Toepfer[1] and Naveed Akbar[1]

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Abstract

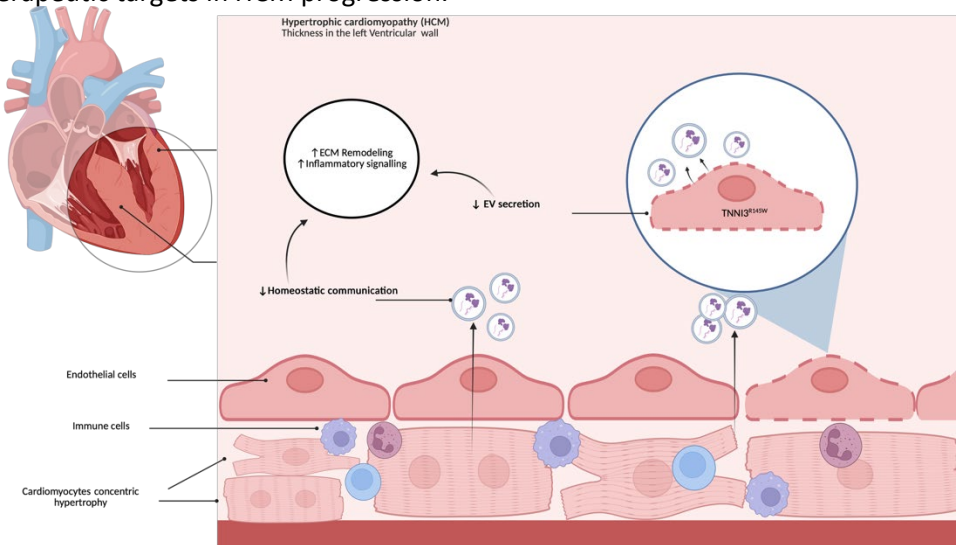
Background: Hypertrophic cardiomyopathy (HCM) is a common inherited disorder (≈1:200), characterised by left-ventricular hypertrophy and caused by sarcomeric gene variants, including cardiac troponin I (TNNI3). HCM also features myocardial fibrosis and immune cell infiltration. The mechanisms tying these non-cardiomyocyte characteristics to sarcomeric mutations are poorly understood. Furthermore, the potential role of extracellular vesicles (EVs) secreted by cardiomyocytes as mediators in HCM pathogenesis is unclear

Methods: Induced pluripotent stem cell–derived left ventricular–like cardiomyocytes (LV-CMs) harbouring the R145W-TNNI3 variant and isogenic controls were generated (N=5 per group). Cells were longitudinally analysed using immunofluorescence, transcriptomics, proteomics, SarcTrack contractility analysis, and Seahorse metabolic assays. EVs were isolated by size-exclusion chromatography and characterised by Nanoparticle Tracking Analysis, ExoView, electron microscopy, Western blotting, and proteomics following MISEV2023 guidelines. UK Biobank plasma proteomics (N=50,000 individuals) were interrogated for HCM patients and intersected with R145W LV-CM cellular and EV proteomic signatures

Results: R145W LV-CMs displayed significant hypertrophy (P=0.0043), increased contraction amplitude (P=0.0027), prolonged contraction duration (P=0.0001), and delayed relaxation (P=0.0001) compared with controls. Seahorse assays revealed increased basal oxygen consumption rates (P=0.0286). Transcriptomic identified 1,080 differentially expressed genes enriched for hypertrophic stress, extracellular matrix (ECM) remodelling, and vesicle/EV signalling pathways. Longitudinal proteomics demonstrated stage–specific dysregulation, with 713 differentially expressed proteins at Day 20 and 1,080 at Day 44, consistently implicating vesicle-transport pathways

EV secretion was significantly reduced in R145W LV-CMs (2-fold; P< 0.0001). Late-stage (Day 44) EV proteomics showed enrichment of ECM/fibrosis and metabolism-associated cargo and depletion of sarcomeric proteins, highlighting dysregulated ECM organisation and vesicle-mediated transport ($P=6.3\times10^{-5}$). Multi-omics implicated interleukin-driven inflammatory pathways. Intersection with UK Biobank HCM plasma proteomics identified histidine-rich calcium-binding protein and stanniocalcin-2 (P< 0.05). Early-stage R145W LV-CM-EVs induced IL-6–mediated inflammatory signalling in left-ventricular fibroblasts and primary monocyte-derived macrophages (P< 0.05)

Conclusion: TNNI3-R145W cardiomyocytes secrete fewer EVs but bare an early-stage immune and late-stage fibrotic signature. These EV-signals promote inflammatory activation in other cardiac cell types, positioning EVs as mechanistic biomarkers and therapeutic targets in HCM progression.



Poster number: 10

TITLE

Functional Analysis Reveals the Unique Cellular Mechanisms of Friedreich's Ataxia Cardiomyopathy

AUTHORS

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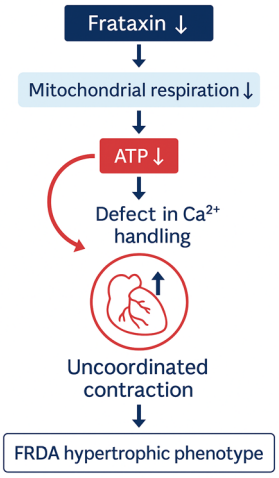
ABSTRACT

Rationale: Friedreich's ataxia (FRDA) is a rare, inherited genetic disease caused by reduced frataxin (FXN) expression, leading to mitochondrial dysfunction and multisystem pathology. Currently, there is no cure for FRDA, and available therapies are limited to symptom management without addressing the underlying molecular cause of the disease. Despite its multisystemic nature, cardiomyopathy is the leading cause of mortality in patients with FRDA. However, the cellular mechanisms driving its development and progression remain poorly characterized, especially in human cardiac tissue. This underscores the need to develop relevant cardiac models to study the molecular processes involved in disease progression.

Methodology: Patient-derived induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) were used to investigate FRDA-associated cardiomyopathy in a human-relevant context. Functional phenotyping included analysis of calcium handling, action potential dynamics, contractility, and mitochondrial respiration. In addition, transcriptomic and signalling pathway analyses were performed to identify disease-associated molecular signatures.

Results: FRDA iPSC-CMs showed marked frataxin deficiency accompanied by mitochondrial bioenergetic failure, prolonged action potentials, impaired calcium handling, and contractile dysfunction. Transcriptomic analysis revealed coordinated dysregulation of pathways related to cardiac development, sarcomeric organization, metabolism, and WNT/EMT signalling, indicating a departure from mature contractile programs. Structural and functional analyses demonstrated sarcomeric remodelling and delayed relaxation kinetics.

Conclusions. Our findings identify mitochondrial dysfunction, along with electrophysiological and contractile abnormalities, as core features of FRDA-associated cardiomyopathy. This work provides a robust platform for future mechanistic studies and for the development of therapeutic strategies targeting cardiomyopathy in Friedreich's ataxia.



Poster number: 11

ICOS Defines Recent Thymic Emigrant T Cells with Distinct Functional Properties

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Medical Science Division, MRC Weatherall Institute of Molecular Medicine, Radcliffe Department of Medicine, University of Oxford, United Kingdom

Naïve T cells, representing antigen-inexperienced cells, are often grouped together despite growing evidence that this population is diverse in terms of cell state and future functional potential. Multiple factors including age, time in periphery, reactivity to self-antigen and exposure to inflammatory stimuli contribute to a layered naïve T cell population. Although several cell surface markers have been used to identify specific naïve T cell subsets, their relationship to each other and their role in regulating T cell responsiveness are unclear. Through a large-scale cell surface proteomic screen and machine-learning (Infinity Flow [1]), we performed an unbiased exploration of the phenotypic heterogeneity of naïve T cells across different age groups (cord, young and old). Following subsequent validation, we identified 10 new cell surface markers that discriminate distinct naïve T cell sub-clusters. One of these was Inducible T Cell Co-stimulator (ICOS, CD278), previously considered to be a marker of activation. When characterising the immune profiles of ICOS+ and ICOS- naïve T cells, we found that the former showed cell surface profiles of recent thymic emigrants (RTE). Consistent with this, ICOS+ naïve T cells contained greater numbers of T cell receptor excision circles and both CD4+ and CD8+ ICOS+ cells expressed an RTE-like transcriptional signature [2]. ICOS+ naïve CD4+ and CD8+ T cells displayed significantly greater chromatin accessibility than their ICOS- counterparts; of note, this included several genes (e.g., *CBLB*) that are upregulated in response to higher TCR tonic signalling. Upon polyclonal stimulation *in vitro*, ICOS+ naïve CD4+ and CD8+ T cells showed lower expression of CD69 (expressed early following TCR activation) and gave rise to less differentiated but more proliferative progenies than ICOS- naïve T cells. Conversely, ICOS- naïve T cells proliferated less, but produced more polyfunctional cytokines and cytotoxic effector molecules. Taken together, these data show that ICOS discriminates distinct naïve T cells with altered functional potential. Ongoing work is directed at providing a better understanding of the underpinning mechanisms directing the differentiation and function of ICOS+ versus ICOS- naïve T cells with the aim of using the findings for the design of novel T cellular therapeutics.

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Poster number: 12

Investigating role of Interleukin-11 (IL11) with Interleukin-6 (IL6) in Atrial Fibrillation

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Background: Atrial fibrillation (AF), the commonest sustained arrhythmia globally, develops via atrial structural remodelling, and is hallmarked by fibrosis. IL11 and IL6 have been implicated in cardiac fibrosis, but their involvement in atrial fibrosis in AF is less well studied in human patients.

Methods: Human atrial tissue (left atrial, LA) biopsies from *25* cardiac surgery patients in sinus rhythm (SR) or with persistent AF (AF) were used for human fibroblast isolation (standard enzymatic digestion protocol). Cells were cultured to passage 3-4. Gene and protein expression of IL11 and its receptor (IL11RA) or IL6 and IL6R were assessed by qPCR and western blot. Myocardial-secreted (coronary sinus, CS) and circulating (peripheral venous, PV) blood from *93* patients in AF or non-AF controls undergoing cardiac procedures, were collected. Serum IL11 and 6 levels were measured by ELISA for pre- and post-ablation, and at 3- and 12-month follow-ups.

Results: IL11 protein levels in circulating (PV, p=0.034) and myocardium-derived (CS, p=0.024) serum were significantly elevated AF patients compared to non-AF controls (Fig. 1A-B). Baseline PV IL11 levels correlated with markers of structural remodeling such as LA dimension (Fig1C), p=0.04, and age, a risk factor of AF development (Fig1D, p=0.04). IL6 levels, however were only elevated in short-lived paroxysmal (pxAF) (p=0.03) and post-cardiac surgery postoperative AF (poAF) cohorts (p=0.04), but not persistent AF (persAF) (Fig 1E-G). At 12months follow-up, serum IL11 and IL6 were significantly lower in those with no AF relapse (Fig. 1H-I). From an *in vitro* cellular level, human left atrial fibroblast (hAFB) *IL11* mRNA expression is significantly upregulated in persistent AF patients (p=0.019), while they were negligible in control patients in sinus rhythm (SR) (Fig. 1J). Immunoblotting revealed protein expression of IL11 was elevated within the human left atrium (Fig 1K-L) in AF. Stimulation of hAFBs with IL11 at 10-50ng/ml range showed elevated profibrotic gene expression such as *Col1A1 and TGFb1* (p=0.04, p=0.03 respectively), and Collagen-1 protein expression in fibroblasts (Fig. 1M).

Conclusions Our results indicate for the first time that myocardial and circulating IL11 and IL6 levels are associated with AF disease, and higher levels are associated with AF-recurrence post AF ablation. While elevation of IL6 is observed in short-term AF subtypes (in paroxysmal and post-operative AF), IL11 increases in a long-standing persistent AF (persAF), and positively correlates with atrial structural remodelling. The data suggest that targeting IL11/IL6 signalling may represent a novel strategy to mitigate atrial fibrosis and improve outcomes in AF. Moreover, AF is associated with activated human atrial fibroblast IL11 signalling at a gene transcription and protein level. Future experiments will assess impact of IL11/6 signalling inhibitors (e.g. LASN01 or tocilizumab) in hAFbs in context of AF to dampen pro-fibrotic phenotypes of hAFbs.

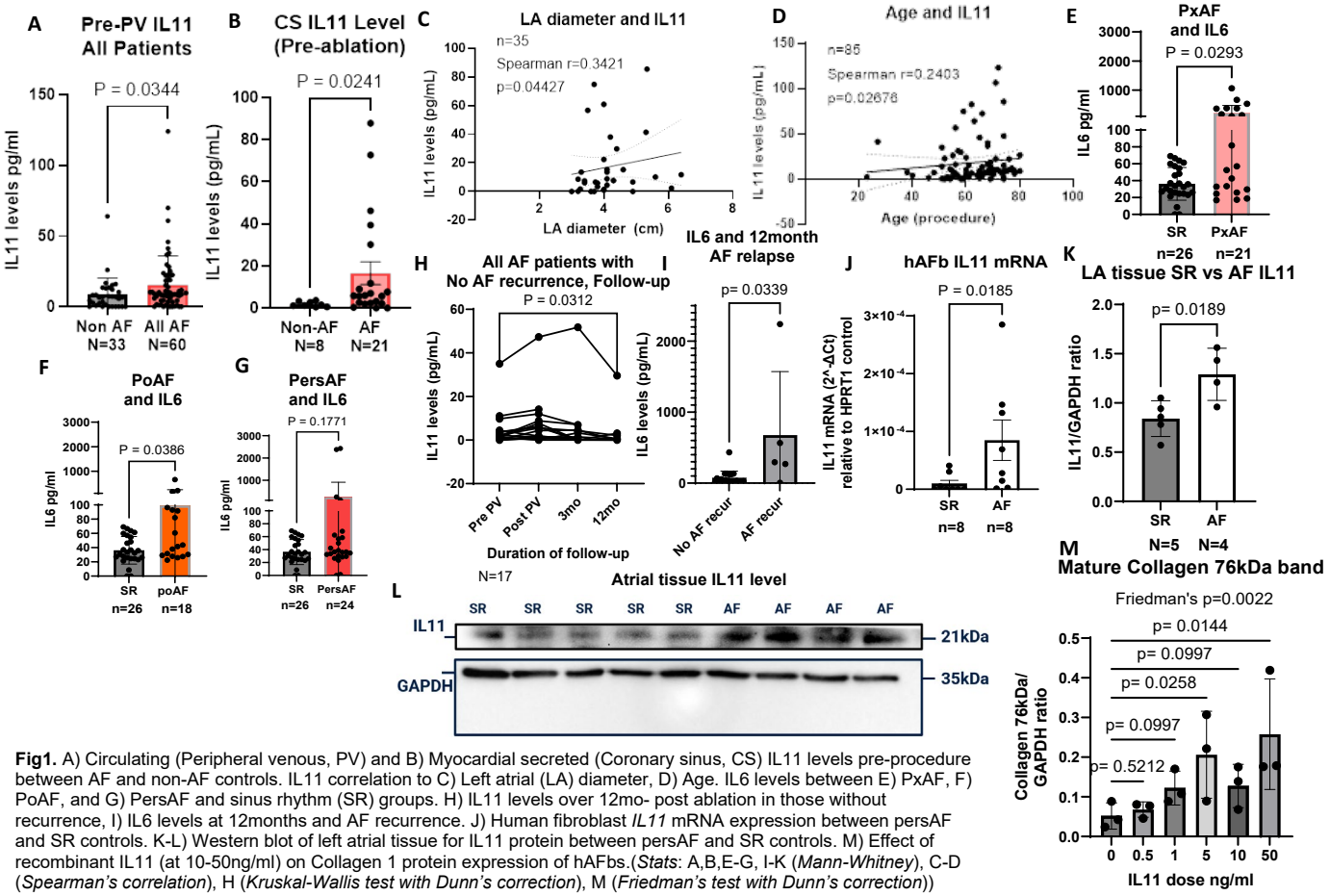

Fig1. A) Circulating (Peripheral venous, PV) and B) Myocardial secreted (Coronary sinus, CS) IL11 levels pre-procedure between AF and non-AF controls. IL11 correlation to C) Left atrial (LA) diameter, D) Age. IL6 levels between E) PxAF, F) PoAF, and G) PersAF and sinus rhythm (SR) groups. H) IL11 levels over 12mo- post ablation in those without recurrence, I) IL6 levels at 12months and AF recurrence. J) Human fibroblast *IL11* mRNA expression between persAF and SR controls. K-L) Western blot of left atrial tissue for IL11 protein between persAF and SR controls. M) Effect of recombinant IL11 (at 10-50ng/ml) on Collagen 1 protein expression of hAFbs.(*Stats*: A,B,E-G, I-K (*Mann-Whitney*), C-D (*Spearman's correlation*), H (*Kruskal-Wallis test with Dunn's correction*), M (*Friedman's test with Dunn's correction*))

Poster number: 13

In vitro evaluation of novel antifibrotic compounds in human atrial fibroblasts

Shuchishmita Maitra (DPhil student) [1], Aaron Johnston[1], Chenhan Ma[1], Val Millar[2], Rana Sayeed[3], Vivek Srivastava[3], George Krasopoulos[3], Nicholas Walcot[3], Priya Sastry[3], Antonios Kourliouos[3], Charles Redwood[1], Paul Robinson[1], Daniel Ebner[2], Svetlana Reilly[1]

[1]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, UK, [2] Target Discovery Institute, [3]Department of Cardiothoracic Surgery, Oxford University Hospitals Trust

Research rationale: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is difficult to treat effectively, partly due to atrial structural remodelling[1]. Atrial fibrosis is a feature of this remodelling and contributes to disease development and persistence[2]. As no therapies directly target fibrosis[3] , this study applied a drug-repurposing approach to uncover new antifibrotic compounds.

Methodology: Human atrial cardiac fibroblasts (ACFs) were isolated from n = 3 patients undergoing cardiac surgery at John Radcliffe Hospital (ethical approval 18/SC/0404). A prior high-throughput drug screen (HTS; >3000 compounds) identified 9 compounds reducing collagen-associated readouts of ≥2 standard deviations relative to vehicle in ≥2 donors (**Fig. 1D-E**). In vitro validation of HTS hits was carried out in ACFs treated with 9 selected compounds for 48 hours. Total collagen content was assessed via collagen assay (Chondrex) and abundance of selected profibrotic markers, fibronectin, collagen I and α-smooth muscle actin (α-SMA) was assessed by Western blotting.

Results: Dose-response curves showed concentration-dependent modulation of collagen production for Drugs A-E (**Fig. 1A**). Total collagen assays showed that 5 of 9 compounds (Drugs B, D, E, F and G) reduced collagen content relative to DMSO-vehicle control (**Fig. 1B**), with larger reductions for Drugs E and G (≈40-50%) and more modest reductions for Drugs B, D and F (≈20-30%), with donor variability. Reduced collagen I protein levels were observed by Western blotting, with decreases of ≈40-50% for Drugs E (10 nM) and G and ≈20-30% for Drugs B and F (**Fig. 1C**). Collagen-reducing compounds also showed reduced α-SMA and fibronectin protein levels (≈20-30% for Drug G). Cell number was largely unchanged except for proteasome inhibitors and the cardiac glycoside at micromolar concentrations.

Conclusions: This study establishes a functional framework for validating new antifibrotic candidates in human ACFs and supports prioritisation of lead drugs for mechanistic and translational investigation.

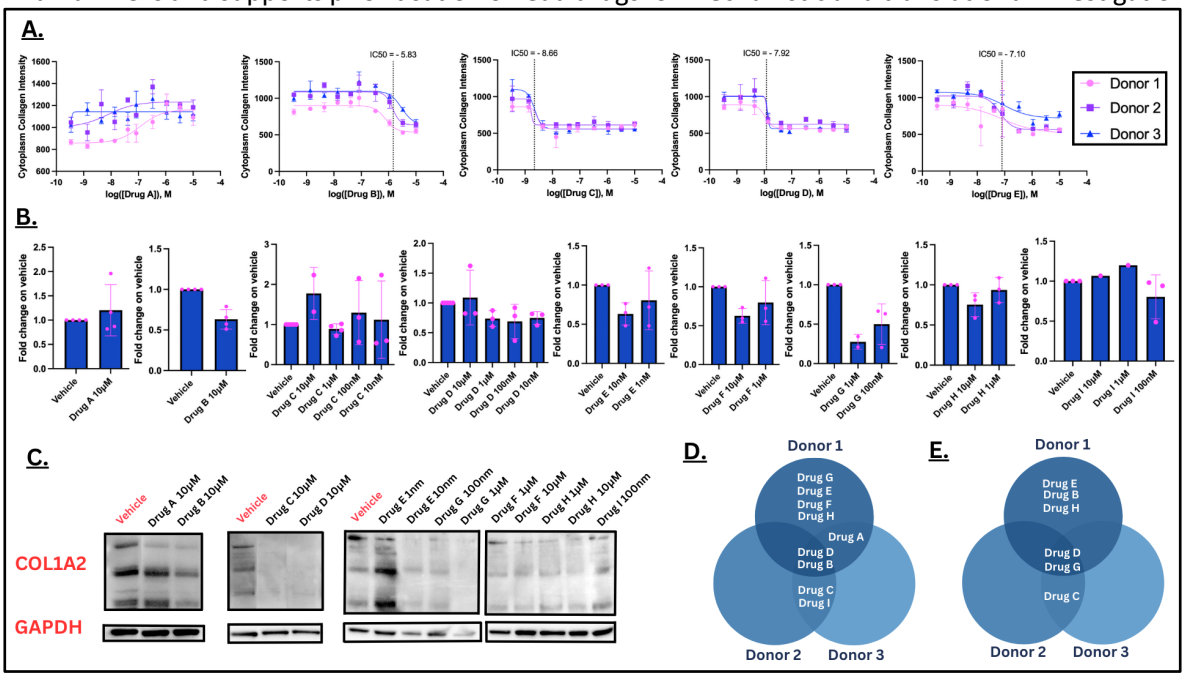

Figure 1. In vitro validation of candidate antifibrotic compounds in human atrial fibroblasts. (A) Dose-response analysis of collagen intensity assessed by HTS; for 5 anonymised compounds in human atrial fibroblasts (n=3). Data are mean ± SEM, n - individual biological donors. **(B)** Total collagen production (collagen assay) in human atrial fibroblasts treated with selected compounds. Data are normalised to vehicle controls and shown as mean ± SEM; n - individual biological donors. **(C)**

Representative Western blots of collagen I (COL1A2) protein in atrial fibroblasts treated with selected compounds. GAPDH was used as a loading control. **(D-E)** Venn diagrams illustrating overlap of hit compounds identified in the HTS (n=3) based on % collagen-positive cell coverage and collagen intensity, respectively, n - individual biological donors.

Poster number: 14

Genetic co-localisation identifies shared genetic architecture for sleep/circadian traits, and prevalent cardiometabolic disease.

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Rationale: Cardiometabolic diseases (CMD), including type 2 diabetes, obesity, hypertension, and fatty liver disease, affect millions worldwide and frequently occur together. Growing evidence indicates that sleep disturbance and circadian rhythm disruption contribute to CMD risk. Conversely, cardiometabolic disease can itself impair sleep and circadian regulation, forming a self-reinforcing cycle. The biological mechanisms underlying this relationship remain unclear.

Methods: We used genetic co-localisation analyses in the UK Biobank to identify genomic loci jointly influencing sleep and circadian rhythm traits alongside cardiometabolic phenotypes. Co-localisation testing evaluates whether multiple traits share a common causal genetic variant within a locus, providing evidence for shared biological pathways. Loci with high posterior probability of shared causality were prioritised and assessed for replication in independent datasets.

Results: Multiple loci showed evidence of shared genetic architecture between sleep/circadian and cardiometabolic traits. One locus demonstrated a high posterior probability of co-localisation with a tightly resolved credible set centred on a single missense variant (rs12140153), replicated across independent cohorts. This variant lies within *PATJ*, a gene previously implicated in genome-wide association studies of body mass index and C-reactive protein. *PATJ* is widely expressed across human tissues, including brain, gastrointestinal, muscle, and immune tissues. In an independent Oxford-based cardiometabolic biobank, carriers of rare deleterious *PATJ* coding variants showed altered serum lipid profiles, particularly sphingolipids.

Conclusions: These findings support shared genetic mechanisms linking sleep and circadian biology with cardiometabolic disease. Large-scale human genetic analyses can help identify novel biological pathways underlying cardiometabolic multimorbidity and highlight potential targets for intervention.

Poster number: 15

Association of inflammation and extent of coronary artery disease in type 2 diabetes (T2D) and acute coronary syndrome (ACS)

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Affiliations:
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AIMS

Complex coronary artery disease (CAD) in diabetes associates with adverse cardiovascular outcomes. High-sensitivity CRP (hsCRP), a marker of inflammation, independently predicts cardiovascular risk. We aimed to explore the relationship between inflammation and CAD extent in T2D.

METHODS AND RESULTS

116 patients presenting with ACS were consented to the INFLAMED study; 62(53.4%) had T2D. hsCRP was performed clinically; median 0(IQR:0-1) days from admission (n=99). At follow-up, hsCRP, IL-6 and IL-18 were measured; median 57(44-72) days from discharge (n=86). CAD extent was stratified by SYNTAX score (low ≤22, high >22).

SYNTAX scores were similar between patients with and without T2D. At admission, hsCRP was higher in T2D (median 3.9(1.4-8.0) vs 2.35(1.1-4.4) mg/L; p = 0.09). hsCRP was significantly higher in patients with high SYNTAX scores (3.9(1.6-8.7) vs 1.9(1.0-4.5) mg/L; p = 0.01), particularly in T2D (5.1(2.6-11.0) vs 2.5(1.6-5.8) mg/L, p = 0.052). After adjustment for age, sex and BMI, high SYNTAX score (β = 0.32, p = 0.002) and T2D (β = 0.25, p = 0.01) were independently associated with higher hsCRP.

At follow-up, hsCRP were similar between groups (median 1.5(0.9-3.6) vs 1.2(0.5-5.0) mg/L, p = 0.223). IL-6 and IL-18 were higher in T2D; median 4.64(2.8-6.35) vs 3.38(2.03-4.76) pg/mL; p = 0.051 and 340(266-422) vs 274(224-369) pg/mL; p = 0.032. After adjustment for age, sex, BMI and CABG, high SYNTAX score was not associated with hsCRP, IL-6 or IL-18 and T2D was only independently associated with IL-18 (β = 0.08, p = 0.044).

CONCLUSIONS

IL-6 and IL-18 were elevated in T2D at follow-up. Inflammation measured by CRP acutely, but not at follow-up, associated significantly with extensive CAD and T2D, suggesting that acute CRP measurement characterises a patient's inflammatory status in CAD.

Poster number: 16

Title

Generation of VCAM-1 Expressing Bioengineered Extracellular Vesicles for Immune Cell Targeting

Authors

Charlotte Hooper[1*], Paul Robinson[1], Zeyu Chen[1], Robin P. Choudhury[1], Naveed Akbar[1]

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Abstract

Myocardial infarction (MI) elevates blood neutrophil and monocyte abundance, with their pro-inflammatory activation correlating with the severity of myocardial injury. Current immunomodulatory strategies struggle to suppress excessive inflammation while effectively promoting resolution. Endothelial cell-derived extracellular vesicles (EC-EV) expressing vascular cell adhesion molecule 1 (VCAM-1$^+$ EVs) are rapidly released into circulation post-MI, where they mobilise cells from the splenic-reserve and induce transcriptional activation prior to recruitment. Neutrophils and monocytes express the VCAM-1 receptor very late antigen-4, enabling targeted interactions. Here, we develop bioengineered VCAM-1$^+$ EVs as a precision tool for therapeutic immunomodulation.

Bioengineered-EC-EVs were generated by incorporating VCAM-1 into the EV-enriched protein CD63, followed by ligation into lentiviral plasmids to generate lentiviral-particles in HEK-293T cells. Human endothelial cells (EA.hy926) were transduced with viral supernatants, followed by puromycin selection. Western blot of transduced lines revealed CD63-enrichment and confirmed VCAM-1 expression. Total EC-EVs (N=4 per group) were isolated via ultracentrifugation and characterised using Nanoparticle Tracking Analysis and Western Blot. Cellular and EV-membranes of transduced lines were subsequently fluorescently labelled with bioluminescence resonance energy transfer-based reporter, PalmGRET, enabling quantitative live-cell imaging. Robust signal was generated in PalmGRET transduced cells versus control (N=4 per group), in isolated PalmGRET-EC-EVs ($P<0.001$) and following uptake into the macrophage cell line RAW 264.7 *in vitro* in a dose-dependent-manner ($P=0.017$).

We have developed VCAM-1$^+$ EVs, providing a novel tool for targeted immunomodulation. Ongoing studies will administer these PalmGRET-VCAM-1$^+$-EC-EVs in a mouse model of MI to investigate their immunoregulatory effects on neutrophils and monocytes.

Poster number: 17

Title: Novel AI biomarker of metabolically unhealthy adipose tissue predicts cardiometabolic risk in patients undergoing CCTA

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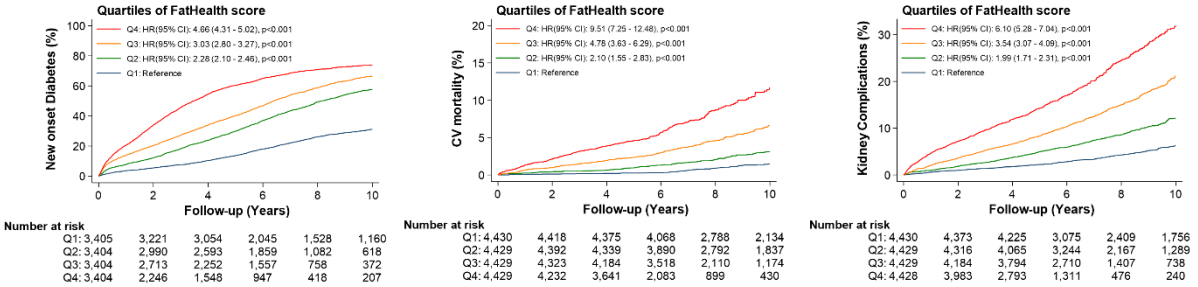
Background: Metabolically dysfunctional adipose tissue (AT) is a key driver of insulin resistance, diabetes, and cardiometabolic complications, yet is poorly captured by current risk scores, blood biomarkers, or anthropometric measures of obesity (Kahn et al., 2006). Inflammation and lipolysis-related changes in AT composition induce measurable shifts in attenuation and texture on coronary computed tomography angiography (CCTA), enabling non-invasive phenotyping from routinely acquired imaging (Antonopoulos et al., 2017).

Aim: To develop and validate a CCTA-based radiomic biomarker (FatHealth) to detect dysglycaemia and adipose tissue dysfunction, and to evaluate its ability to predict incident diabetes and cardiometabolic outcomes.

Methods: Radiomic features were extracted from pericardial and epicardial adipose tissue on CCTA and integrated into the FatHealth score, trained to discriminate individuals with dysglycaemia from non-diabetic controls. Clinical validation was performed across three centres using oral glucose tolerance testing (OGTT). Prognostic performance was assessed in the Oxford Risk Factors and Non-Invasive Imaging (ORFAN) cohort (n=17,137 for mortality and complications; n=13,737 for incident diabetes).

Results: In the clinical validation study, higher FatHealth was associated with an adverse glycaemic profile and a higher likelihood of dysglycaemia on OGTT. In ORFAN, increasing FatHealth quartiles were associated with a graded increase in long-term risk. Compared with the lowest quartile, the highest FatHealth quartile showed higher risk of all-cause mortality (HR 6.21, 95% CI 5.31–7.26), cardiovascular mortality (HR 9.51, 95% CI 7.25–12.48), incident diabetes (HR 4.66, 95% CI 4.31–5.02), kidney complications (HR 6.10, 95% CI 5.28–7.04), and eye complications (HR 4.46, 95% CI 3.34–5.96; all p<0.001).

Conclusion: A CCTA-based radiomic biomarker of adipose tissue dysfunction identifies dysglycaemia and robustly predicts incident diabetes, mortality, and cardiometabolic complications, supporting opportunistic imaging-based risk stratification.



Poster number: 18

Title: Epigenetic editing of therapeutic T cells

Authors: Anna-Sophie Haselon[1] (DPhil student), Bora Ozcan[1], James Davies[1], Fadi Issa[2], Ronjon Chakraverty[1]
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Abstract:
Rationale: CRISPRoff is a dCas9 based epigenome editor that can induce heritable repression of gene expression through methylation rather than DNA-double strand breaks (1), presenting a potentially safer alternative for clinical applications. Chimeric antigen receptor (CAR)-T cell therapy commonly causes side effects including cytokine release syndrome, neurotoxicity, and on-target off-tumour toxicity, facilitated through their secretion of cytokines such as GM-CSF and expression of migratory molecules including VLA-4 (2, 3, 4).
Methodology: Primary human naïve T cells were activated and nucleofected with CRISPRoff mRNA and several gRNAs targeting either *ITGA4* or *CSF2*. The promoter sequences of these genes could be distinguished by their CpG content (*ITGA4* high and *CSF2* low) (5). The effect of each gRNA on protein expression of VLA-4 (CD49d) and GM-CSF and on CpG methylation at the gene's promoter region was tested.
Results: Targeting CRISPRoff to *ITGA4* reduced CD49d protein expression on average by over 50% compared to a control, non-targeting gRNA and was similar to a CRISPR nuclease-mediated knockout. *ITGA4* repression was stable across 24 days and an estimated 11 cell doublings. CRISPRoff targeting induced sustained methylation of the *ITGA4* promoter region versus controls, a methylation signature not observed in non-manipulated naïve T cells. Targeting CRISPRoff to *CSF2* (where the promoter region lacked CpG) reduced GM-CSF expression on average by more than 30% compared to a non-targeting gRNA; however, the corresponding increase in promoter methylation compared to controls was less pronounced.
Conclusion: Heritable repression of protein expression can be induced through transient delivery of CRISPRoff into primary human T cells targeting a gene of therapeutic interest. We are now exploring the use of a lentivirus-based platform to induce multiplex CRISPRoff-based epigenetic editing for multiple therapeutic targets.

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Poster number: 19

Plasma Extracellular Vesicles in People with Diabetes Following Acute Myocardial Infarction

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Rationale: People with diabetes experience disproportionately poor outcomes following myocardial infarction (MI), despite contemporary glucose-lowering and cardiovascular therapies, highlighting a major unmet need for improved prognostic markers and mechanistic insight. Extracellular vesicles (EVs) regulate post-MI immune and vascular responses. We investigated whether diabetes alters circulating plasma EV profiles following MI in clinical cohorts, and whether metabolically stressed endothelial cells develop pro-inflammatory and dysfunctional phenotypes that may mechanistically underpin these EV-signatures.

Methods: Platelet-poor plasma EVs were analysed from N=134 patients presenting with acute myocardial infarction, with (N=67) and without (N=67) diabetes with temporally resolved sampling from acute presentation through to recovery. Cardiac magnetic resonance imaging in the acute phase and 6 months later with late gadolinium enhancement were used to assess infarct size and cardiac function. EVs were profiled using a high-throughput EV-Array targeting 40 EV-associated proteins, spanning endothelial, immune, cardiomyocyte and metabolic pathways, enabling multivariate and longitudinal analyses of diabetes-associated EV signatures following MI. Human coronary artery vascular endothelial cells were exposed to diabetic-relevant metabolic and inflammatory stress, including high glucose (20 mM), mixed fatty acids (100–1000 µM oleate, palmitate, linoleic and α-linolenic acids; OPLA;45:30:24:1, POLA;44:45:10:1), and tumour necrosis factor-α (TNF-α, 1 or 10 ng/mL) using high throughput robotics with bulk RNA-sequencing. Additionally, endothelial viability, inflammatory cytokine release, expression of vascular activation, lipid-handling markers, EV-production were assessed using multiplex immunoassays.

Results: Patients with diabetes demonstrated significantly greater left ventricular ejection fraction recovery compared to non-diabetics (5.4% v 1.9% improvement, $p=0.028$). Patients with diabetes exhibited distinct circulating EV-profiles following MI, with significant upregulation of the glucose transporter GLUT-1 (1.4-fold, FDR < 0.01), the EV-associated protein Flotillin-1 (2-fold, FDR < 0.05), and myosin-related markers. In parallel, endothelial cells exposed to metabolic stress alone maintained viability (>90%), whereas combined metabolic and inflammatory stress significantly increased interleukin-6 (IL-6) secretion (1.8-fold increase, $p<0.001$). However, high lipid exposure in the presence of TNF-α reduced expression of the endothelial activation marker VCAM-1 (0.65-fold reduction, $p<0.0001$).

Conclusions: Diabetes is associated with alterations in circulating plasma EV profiles following myocardial infarction. Complementary mechanistic studies demonstrate that combined metabolic and inflammatory stress drives endothelial inflammatory dysfunction, providing a plausible biological basis for diabetes-associated EV signatures.

Poster number: 20

Title: Re-distribution of histone H4 lysine 16 acetylation in macrophages following pro-inflammatory activation

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Research Rationale: Myeloid cells are crucial effectors of the innate immune response, providing host-defence against pathogens and tissue damage. Macrophage phenotype is tightly regulated through differential transcription factor binding in response to internal and external signals, which establish and modify the epigenetic landscape, including chromatin accessibility, histone modifications, and DNA methylation. In this study, we systematically profile global histone modifications in macrophages using quantitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) and perform Cleavage Under Targets and Tagmentation (CUT&Tag) to map their genomic distribution following pro-inflammatory 'M1' activation.

Methodology: Monocytes from healthy donors (n=3) and bone marrow cells from wild-type mice (n=3) were isolated, differentiated into macrophages and stimulated with lipopolysaccharide (LPS) and interferon-gamma (IFN-γ) (M1). Histones were acid-extracted, propionylated and digested using trypsin prior to analysis by LC-MS/MS. CUT&Tag targeting H4K16ac was performed, and the resulting data were analysed using the CATCH-UP pipeline[1].

Results: LC-MS/MS revealed a 5% reduction in global H4K16ac following M1 stimulation ($P < 0.01$), which was conserved across species ($P \leq 0.01$). Genome-wide quantile analysis of CUT&Tag signal showed a broad decrease in H4K16ac across low- and intermediate-signal chromatin in M1 samples, consistent with LC-MS/MS. Differential peak analysis (adjusted $P < 0.05$) identified 635 regions with altered H4K16ac, characterised by increased enrichment at promoter-proximal regions and preferential loss from gene bodies and other non-promoter regions in M1 versus M0 conditions.

Conclusions: LC-MS/MS identified significant changes in the global abundance of histone modifications, specifically a reduction in H4K16ac, following pro-inflammatory activation of macrophages. While genome-wide analyses confirm broad depletion of H4K16ac under M1 conditions, differential peak analysis identified promoter-proximal regions with increased H4K16ac relative to M0 macrophages, indicating a re-distribution of signal rather than a net gain of acetylation. These findings suggest that pro-inflammatory activation drives a global re-organisation of H4K16ac toward promoter-associated chromatin.

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Poster number: 21

Title: The interplay of systemic and local coronary inflammation in cardiovascular risk prediction

Authors: Kenneth Chan[1,2], Cheng Xie[1,2], Elizabeth Wahome[1], Jagat Chauhan[1], Daniel Foran[1], Ileana Badi[1], Claudia Monaco[3], Jennifer Cole[3], David Ahern, PhD[3], Antonio Berretta[1], Leanne Eveson[1], Ioannis Akoumianakis[1], Bowen Xiao[1], Christos P Kotanidis[1], Ikboljon Sobirov[1], Alexios S. Antonopoulos[1], Henry West[1], Evangelos K. Oikonomou[1,4], Damaris Darby[1], Edward Nicol[5,6], Jonathan Weir-McCall[5,6], Ronak Rajani[7], David Adlam[8], Jonathan Rodrigues[9], Nicholas Screaton[10], Attila Kardos[11], John P. Greenwood[12], Nikant Sabharwal[2], Andrew Kelion[2] Francesca Pugliese[13,14], Steffen E. Petersen[13,14], Yogesh Sohan[15], Pete Tomlins[15], Muhammad Siddique[15], Cheerag Shirodaria[2,15], Brittany Weber[16], Daniel Huck[16], Ron Blankstein[16], Milind Desai[17], Bernard J. Gersh[17,18], Stephan Achenbach[19], Eve Fryer[20], Ian Roberts[20], Peter Libby[16], Stefan Neubauer[1,2], Keith M. Channon[1,2], John Deanfield[21], Charalambos Antoniades[1,2] on behalf of the ORFAN Consortium

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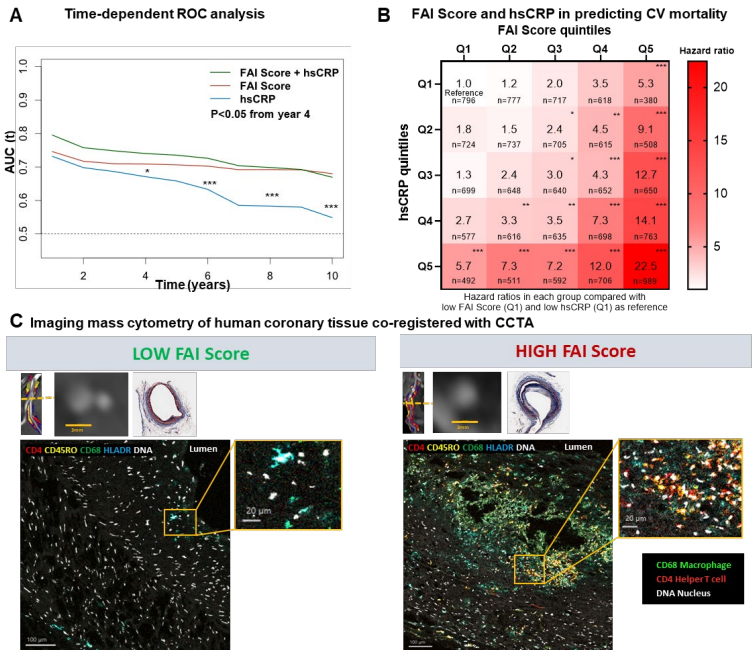
Background: Coronary inflammation is a therapeutic target for cardiovascular prevention. We explore the clinical and molecular interplay linking systemic inflammation (using the high sensitivity CRP (hsCRP) and local coronary inflammation (using the Fat Attenuation Index (FAI) Score from coronary computed tomography angiography (CCTA)) to cardiovascular risk.

Methods: The study enrolled 16,445 individuals undergoing routine CCTA for chest pain evaluation. FAI Score and hsCRP were measured at baseline, and the participants were followed over a median[IQR] of 5.1[3.5-6.6] years. In separate complementary cohort studies, internal mammary artery biopsies were obtained from patients undergoing cardiac surgery, and post-mortem coronary artery samples were obtained following post-mortem CCTA, to understand the nature of local coronary inflammation captured by hsCRP or FAI Score.

Results: Both hsCRP and FAI Score demonstrated independent predictive value for cardiovascular mortality particularly in the first 3-year follow up, while FAI Score alone had sustained predictive value over 10 years.(**A**) Patients in the highest quintile of both hsCRP and FAI Score experienced a 22-fold higher risk of cardiovascular mortality vs the lowest quintile.(**B**) Arterial RNA sequencing studies revealed that both biomarkers captured features of innate immunity, but FAI Score was specific for adaptive and particularly T-cell immunity, a finding confirmed on imaging mass cytometry of human coronary arteries.(**C**)

Conclusions: Assessment of systemic and local coronary inflammation provides complementary insights into the immune components of the residual inflammatory risk, tailored to the target population. Local coronary inflammation using FAI Score on CCTA identifies high-risk individuals independently from coronary disease and hsCRP, providing a powerful tool in preventive cardiology.



Poster number: 22

Human Endogenous Lentiviral Particles (HELP) for the Delivery of CRISPR Ribonucleoprotein Complexes

Shahzaib Tariq[1], Soumyasree Bhattacharyya[1], Daniel C. Farley[2], Deborah R. Gill[1], Stephen C. Hyde[1], and Jakob H. Haldrup[1]

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Genome editing offers enormous therapeutic potential to treat rare diseases, but current delivery strategies face many challenges, Direct delivery of CRISPR ribonucleoprotein (RNP) complexes via Virus-like Particles (VLPs) offers an attractive solution. We utilise VLPs derived from lentiviral vectors that contain no genome, for transient delivery of RNP complexes. These degrade within 3 days, reducing the risks of prolonged CRISPR-Cas expression, including off-target editing, chromosomal translocations, copy number alterations, chromothripsis, and unwanted genomic integration.

A key challenge using VLPs is the potential for host immune responses towards the viral components and/or therapeutic. We hypothesise that host immune responses can be mitigated by replacing viral components with biologically active homologues repurposed from the human genome.

Using integrative bioinformatic approaches we identified human retrotransposons and human endogenous retroviruses (hERVs). Multiple homologues were repurposed to generate an array of human endogenous lentiviral particles (HELPs). HELP performance was assessed in a HEK293T reporter cell line, enabling rapid quantification of CRISPR-induced gene knockouts.

Initially, four HELP configurations were developed, with gene knockout rates of up to 80%, demonstrating the feasibility of the approach. Further modifications included incorporation of membrane-anchoring motifs, to enhance gene editing. We also developed a scalable manufacturing process to yield more potent VLP preparations, capable of high gene knockout rates (70-90%) with a >2-fold reduction in dosage. This process was readily implemented at >1 L scale and uses unit operations transferrable to commercial manufacturing.

These results establish HELPs as a robust and scalable genome editing delivery platform suitable for *in vivo* evaluation and immune profiling.

Reporter D2eGFP knockout efficiencies of Human Endogenous Lentiviral Particle (HELP) configurations with and without the incorporation of membrane anchoring motifs. Data represent mean ± SD; n = 3 biological replicates. Statistical significance was assessed using unpaired t-tests with Welch's correction (* $p < 0.05$). Ns = no significance.

Poster number: 23

Gastric Epithelial Remodelling as an Early Defence Against *Helicobacter pylori*

Lei Deng (postdoc), Jan Bornschein, Anna Aulicino, Marta Jagielowicz, Verena Lentsch, Vy Wien Lai, Jun Sung Park, Tarun Gupta, Xiao Qin, Paula Gomez Castro, David Fawkner-Corbett, Vincent Saint-Martin, Hannah Chen, Agne Antanaviciute, Alison Simmons

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Research Rational

Helicobacter pylori (*H. pylori*) infects over one-third of adults in the United Kingdom, causing lifelong gastric inflammation and increasing stomach cancer risk. Some infection-induced epithelial changes persist after bacterial clearance.

Our research investigates how gastric epithelial cells respond to *H. pylori* infection and how these defence responses may drive cancer-associated signalling.

Methodology

Primary human gastric epithelial cells were isolated from antrum biopsies of *H. pylori*–negative individuals and patients with *H. pylori*–associated chronic gastritis. Spatial transcriptomic profiling was used to define epithelial cell-type–specific H. pylori colonisation and gene regulation in infected and neighbouring cells. Single-cell multiome (ATAC + RNA) analysis was performed to characterise transcriptional and epigenetic regulation across epithelial populations. In addition, a primary organoid-derived mucosoid model was employed to investigate H. pylori virulence factors and host pathogen recognition receptors mediating epithelial defence signalling.

Results

We found that *H. pylori* preferentially colonise specific gastric epithelial cells, particularly foveolar and proliferative cells, and trigger significant signalling regulations in these cells and their surrounding cells. In stomach biopsy samples from infected patients, we identified two previously unrecognised epithelial cell populations associated with infection, showing features of bacterial defence and epithelial remodelling. We also identified bacterial flagellin as a key factor that activates host defence signalling in epithelial cells through the immune receptor TLR5.

Conclusions

This study identifies epithelial remodelling responses that mediate host defence against *H. pylori* during early chronic gastritis. We show that *H. pylori* preferentially colonises specific gastric epithelial cell types and alters local signalling networks. Bacterial flagellin is identified as a key trigger of early epithelial defence via TLR5, providing insight into *H. pylori* persistence and infection-associated gastric cancer risk.

Poster number: 24

Automated IHC Detection and Spatial Statistical Analysis for Validation of Spatial Transcriptomic Experiments

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MOTIVATION: Recent years have seen an explosion in spatial transcriptomics (ST) technologies, creating a need to validate ST findings at a protein level. Whilst there are emerging spatial proteomics approaches, immunohistochemistry (IHC) is an established, cost-effective option. This work demonstrates a proof of concept for using IHC to validate ST findings.

METHODS: The ST data for validation was produced using 10x Xenium platform on 30 human bone marrow samples, spanning normal, n=5, and myeloproliferative neoplasia (MPN), n=25 (including myelofibrosis, n=11). An IHC panel was used on a subset of the samples (n=24): RET40F, CD3, CD20 and CD79A. Positive cells were detected with QuPath (CD3, CD20, CD79A) and using a bespoke computer vision approach for RET40F (developed to only detect positive nucleated cells). Following this, IHC images were registered with DeeperHistReg, using RET40F as a reference, transforming detections to a shared coordinate space for further analysis.

RESULTS: Area-normalised counts of positive cells were compared to area-normalised cell counts from ST, showing good correlation (Pearson: CD3 vs T-cells r=0.72, CD20 vs B-cells r=0.85, CD79A vs B-cells r=0.77, RET40F vs erythroids r=0.88; all $p<0.05$). Image registration had satisfactory performance in just over half of the cases. A range of spatial statistical measures were used, including Wasserstein distance, average nearest neighbour and Ripley's K. The spatial IHC analysis was supportive of observations within the ST data, showing less association between lymphocytes and erythroids in myelofibrosis, compared to non-fibrotic cases.

CONCLUSIONS: This work demonstrates a proof of concept for using IHC as a method for ST validation. It performs very well for cell quantification, however spatial inference is limited by registration performance - to circumvent this, we recommend considering using consecutive sections or larger external validation cohorts.

Poster number: 25

Visualizing tight junction formation in developing human gut with STED super-resolution microscopy

Dimitrios Ioannidis (DPhil)[1,2], Dr Julian Pietsch[1], Dr David Fawkner-Corbett[2], Marta Jagielowicz[2], Dr Agne Antanaviciute[2], Dr Chloe Hyun-Jung Lee[2], Prof. Alison Simmons[2], Dr Karina Pombo-Garcia[1,2]

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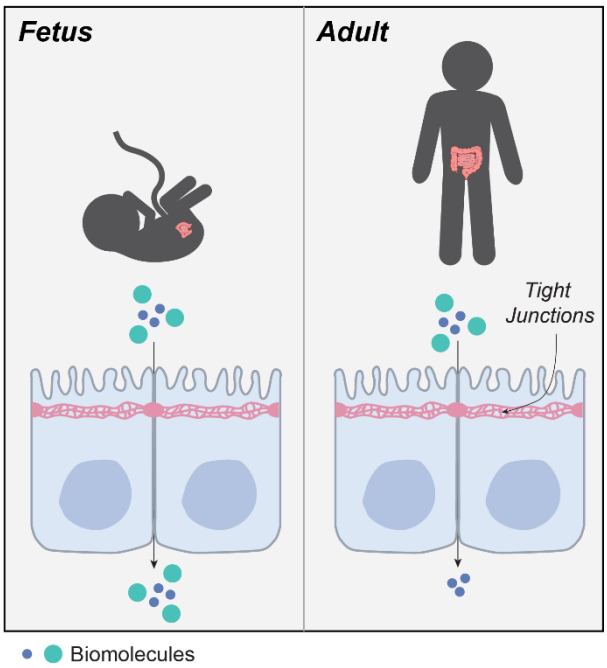
Abstract:

The intestinal epithelium is a selectively permeable barrier that balances nutrient absorption with protection against microbial intrusion. Tight junctions (TJs) are cell to cell adhesion complexes responsible for the permeability of the barrier, and their disruption often leads to disease. Despite their importance in barrier formation and maintenance, little evidence exists on how TJs form and mature during human intestinal development. Here, we visualise the development of TJ architecture at the nanoscale using super resolution stimulated emission depletion (STED) microscopy in human foetal and adult tissue and matched organoids. Functional assays assessing TJ permeability, on patient derived organoids, indicate that early foetal junctions might not be fully functional. Understanding the physiological process of TJ formation and maturation could shed light in the pathogenesis of diseases of prematurity, associated with TJ malfunction, such as necrotizing enterocolitis.

Graphical Abstract:



Poster number: 26

Title: Predicting spatial transcriptomics from histology images of inflammatory bowel disease

Authors: Kexin Xu[1,2*], Jun Park[1,2], Colleen McGregor[1,3], Tarun Gupta[1,3], Esther Bridges[1], Verena Lentsch[1], David Fawkner-Corbett[1,4], Vy Wien Lai[1,2], Karolina Kunnapuu[2,3], Zinan Yin[1], Zoe Christoforidou[1], Marta Jagielowicz[1], Najib Sharifi[1,2], Ruchi Tandon[5], Jan Bornschein[1,3], Katherine Baker[6], Mark Bignell[6], Bruce George[6], Renuka Teague[7], Sorayya Moradi[7], Eve Fryer[5], Michael Vieth[8], Alison Simmons[1,3], Hashem Koohy[1,2], Agne Antanaviciute[1,2] (*presenting author is a DPhil student)

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Abstract:
Inflammatory bowel disease (IBD) is characterised by chronic inflammation in the gastrointestinal tract. Its diagnosis, prognosis, and treatment are challenging due to a lack of clear biomarkers.

Spatial transcriptomics (ST) could identify biomarkers, but its clinical application is inhibited by costs. To overcome this, deep learning has been used to predict ST from commonly available H&E images. While existing models focused on cancers, we developed a model for IBD.

Deep learning was applied on ST data of IBD and healthy controls from Visium and Xenium technologies. 14 H&E foundation models were each applied on H&E images to predict genes and cell types.

Our pipeline yielded non-inferior performance to existing studies. Genes in the Xenium 480 and 5k panels were predicted with a mean Pearson's correlation (*R*) of around 0.6, including disease-specific genes, such as inflammation markers. Moreover, we derived 16 cell types from Xenium data and predicted them with a mean *R* above 0.6, including B-cells and T-cells. Remarkably, the model achieved a mean *R* of just below 0.5 in predicting 30 cell subtypes, including CD4+ T-cells and macrophages MMP12^{+}. The model performed much better on Xenium compared to Visium data, likely due to the higher sensitivity of the former.

In summary, we applied deep learning to predict disease-specific genes and cell types from H&E images of IBD. With limited ST data on IBD, our model provided an avenue to run "virtual" ST studies with H&E images, offering potential diagnostic, prognostic, and therapeutic values.

Poster number: 27

Title

High-Efficiency *In Vivo* Genome Editing of *SERPINA1* Using Homology-Independent Targeted Integration (HITI)

Authors

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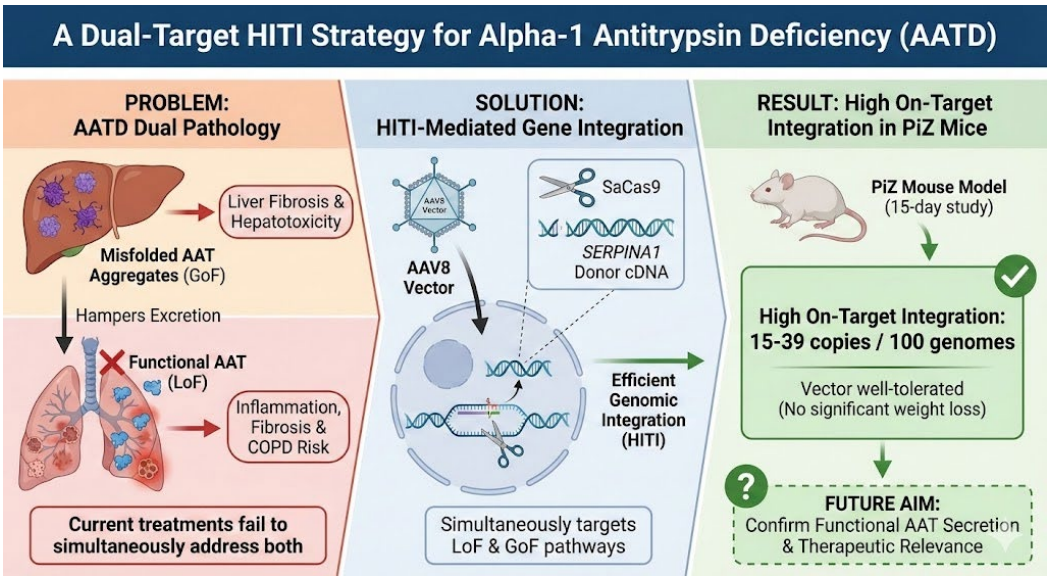
Mutations in *SERPINA1* drive alpha-1 antitrypsin (AAT) deficiency which is a complex therapeutic target characterised by dual pathogenesis: Gain-of-Function (GoF) of AAT to form aggregated polymers in the liver, hampering secretion of AAT, resulting in the Loss-of-Function (LoF) in the lungs, primarily regulating trypsin. This LoF creates an inflammatory cascade that over time results in fibrosis of the lungs generating a predisposition to chronic obstructive pulmonary disease.

Current treatments, such as AAT replacement therapy or treatments in development such as RNA interference therapeutics, fail to simultaneously treat both LoF lung pathology and GoF liver pathology. Here we address both aspects of AAT deficiency using homology independent targeted integration (HITI) to efficiently integrate therapeutic *SERPINA1* cDNA and arrest misfolded polymer expression *in vivo*.

The PiZ mouse model exhibits multiple (8-16) copies of human mutant "Z" allele for *SERPINA1* (PiZ). Mice were given a total dose of 1.2E14 GC/kg of AAV8 with either SaCas9 or AAT donor genomes in a 1:1 ratio, or a vehicle control. Body weights were monitored throughout the 15-day study and endpoint serum and tissue samples collected for fluorescent microscopy and DNA analysis. No significant difference in weight was observed between dosed animals and vehicle controls indicating the vector was well-tolerated. On-target genomic analysis of integrated cDNA showed 15 copies per 100 diploid genomes (n=11) and a second assay, more tolerant to insertions and deletions at the probed locus, suggested a higher integration of 39 copies per 100 genomes (n=3/11). This murine study shows HITI can achieve high on-target *in vivo* editing. Work is ongoing to confirm the editing can provide sufficient functional AAT secretion to be therapeutically impactful.



Poster number: 28

Title: **Using induced pluripotent stem cells (iPSC) to develop a model for ABCA3 surfactant deficiency**

Authors: AMA Glasgow, H Dolatshad, SC Hyde, DR Gill

Departmental Affiliations: NDCLS, Radcliffe Department of Medicine, University of Oxford, UK

Abstract:

Mutations in lipid transporter ATP-binding cassette A3 (ABCA3) can cause lethal respiratory distress in neonates, interstitial lung disease in children and progressive pulmonary fibrosis in adults. There are currently no effective cures or treatments for the underlying cause. We are developing a lentiviral vector, rSIV.F/HN, to treat lethal ABCA3 surfactant deficiency at birth. Research in this area is hindered by inadequate access to robust models of the key lung cells involved, alveolar type 2 (AT2) cells, which are difficult to access from patients especially in the rare disease setting. We are using induced pluripotent stem cells (iPSC) to derive AT2-like cells (iAT2) for disease modelling and vector testing.

We used human iPSC lines, either ABCA3 wild-type (WT) or ABCA3 p.L101P (mutation affecting protein trafficking). These were differentiated to iAT2 cells and maintained as organoids in 3D culture according to published methods (PMID:31732721, illustrated in Figure 1). Western blotting of L101P mutant AT2 cell lysates showed reduced ABCA3 expression and a defect in ABCA3 protein processing. To measure ABCA3 lipid transporter function, 2D iAT2 cultures were incubated with fluorescently labelled phospholipids (24 hr), then assayed by flow cytometry. The L101P iAT2 cells showed reduced fluorescence intensity relative to WT iAT2, indicating reduced ABCA3 function. Preliminary studies using rSIV.F/HN expressing EGFP showed delivery to approximately 20% of iAT2 cells. We are now evaluating the ability of rSIV.F/HN to deliver ABCA3 and rescue the phenotype of ABCA3 mutant cells to generate proof-of-principle data for gene therapy to treat ABCA3 surfactant deficiency in babies.

Figure 1

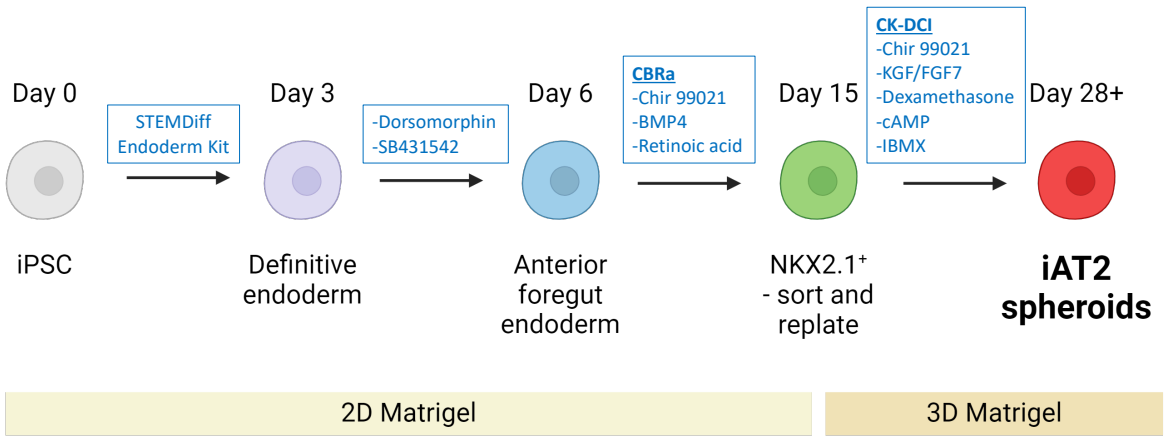


Figure 1. Schematic summarising the key steps in directed differentiation of iPSC to iAT2.

Poster number: 29

Title: ***Natriuretic Peptides Reverse Vascular Endothelial Insulin Resistance and Ameliorate Dysregulated Redox Signalling when Administered Alongside Insulin in Human Atherosclerosis***

Authors: Daniel Foran[1*], Ileana Badi[1], Surawee Chuaiphichai[1], Murray Polkinghorne[2], Jagat Chauhan[1], Andrea D'alessio[3], Priya Sastry[3], Antonios Kourliouros[3], Nicholas Walcot[3], Vivek Srivastava[3], George Krasopoulos[3], Rana Sayeed[3], Alexios Antonopoulos[1], Keith Channon[1], Ioannis Akoumianakis[1], Charalambos Antoniades[1, 4]

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**DPhil Student*

Aim: Patients with atherosclerosis and type 2 diabetes (T2DM) on insulin therapy have poor cardiovascular outcomes. Atherosclerosis patients with and without T2DM exhibit vascular endothelial insulin resistance (VIR). When exposed to insulin, pathological endothelial signalling activates NADPH oxidase (NOX) and uncouples endothelial nitric oxide synthase (eNOS), resulting in excess superoxide production and consequently, vasoconstriction, inflammation, and oxidative stress. DPPIV inhibitors ameliorate this effect ex vivo but do not confer prognostic clinical benefits. Natriuretic peptides (BNP and ANP) are DPPIV substrates that may modulate endothelial insulin and redox signalling.

Methods: Blood, internal mammary artery (IMA) and saphenous vein (SV) were collected from 391 adults undergoing coronary bypass surgery. Plasma BNP and insulin were measured by ELISA. DNA was extracted from whole blood and sequenced. Vessel rings were incubated in 4 conditions (control, insulin, BNP/ANP, insulin & BNP/ANP). Superoxide production was measured in IMAs via chemiluminescent luminometry. Endothelial function was quantified in SVs via vasomotor studies. Western blotting quantified activation of signalling molecules (AKT, ERK, eNOS, IRS1, RAC1, p47-Phox). Patients were followed up for 10 years.

Results: Insulin impairs endothelium-dependent vasorelaxation ($p=0.01$) whilst BNP with insulin improves endothelium-dependent vasorelaxation ($p=0.04$). Insulin increases IMA resting ($p<0.001$) and NOX-derived ($p<0.001$) superoxide production and uncouples eNOS ($p=0.027$). BNP combined with insulin reduces resting ($p=0.0002$) and NOX-derived (p0.012) superoxide production, and recouples eNOS (p0.013). We see the same results with ANP. Insulin alone increases endothelial ERK ($p=0.004$) and IRS1 ($p=0.03$) phosphorylation and RAC1 and p47-Phox activation and translocation ($p=0.03$) but does not activate AKT or eNOS. BNP with insulin increases AKT ($P=0.004$) and eNOS ($p=0.03$) phosphorylation and reduces IRS1 phosphorylation ($p=0.008$) and RAC1 and p47-Phox activation and membrane translocation ($p=0.01$ and $p=0.03$). A SNP causing increased *nppb* expression and plasma BNP (rs198983) is associated with increased NOX-derived superoxide ($p=0.028$) and increased major adverse cardiovascular event rates ($p=0.03$) in diabetics.

Conclusion: Natriuretic peptides sensitise the arterial wall to insulin and ameliorates pathological redox signalling related to VIR. BNP and ANP could be used to reverse the pro-atherogenic profile of insulin treatment in T2DM.

Poster number: 30

Title: Iron deprivation impairs human B cell activation, proliferation and differentiation *in vitro*

Authors

Giulia Pironaci[1] (DPhil student), Shamsideen Yusuf[1], Dana Costigan[1], Maria Obregon Comino[1], Charlotte Buckley[1], Hannah Murray[1], Alexandra Preston[1], Andrew Armitage[1], Elizabeth Clutterbuck[2], Nicole Stoffel[3], Hal Drakesmith[1]

Affiliations

[1] MRC Weatherall Institute of Molecular Medicine, Radcliffe Department of Investigative Medicine, University of Oxford, United Kingdom

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Abstract

Human genetic studies and murine models demonstrate that iron availability contributes to effective adaptive immune responses, including to vaccines. However, the impact of iron deficiency on human B-cells, remains poorly understood. This project aims to study the mechanisms through which iron regulates human B-cell responses *in vitro*.

We used multiple different culture systems to stimulate human B cells polyclonally under both T cell–dependent (via CD40 receptor) and T cell–independent conditions for 3-7 days. Iron availability was modulated either by using media with modified iron concentrations or by adding the intracellular iron chelator deferiprone (DFP). B-cell activation, proliferation, and differentiation into antibody-secreting plasma cells and memory B-cells were assessed.

B cells cultured in iron-free medium retained the ability to divide and differentiate, although activation was modestly reduced. In contrast, DFP treatment significantly impaired T-cell dependent B-cell activation as assessed by expression of CD71 and CD86, B-cell proliferation as measured by CTV dilution, and differentiation into IgG+CD38+ antibody-secreting cells. Notably, DFP treatment also suppressed activation, proliferation of naïve B-cells and their differentiation into CD27+ memory cells under T-cell independent activation conditions. Finally, supplementation with ferric ammonium citrate counteracted deferiprone, restoring functional B-cell responses.

These results suggest that intracellular iron availability is critical for effective human B-cell responses *in vitro*, including activation, proliferation, antibody production and memory formation. While these data provide initial insights, they are limited to *in vitro* systems. Further studies are warranted to establish whether iron deficiency has a significant impact on vaccine responses in humans. Understanding how micronutrient status shapes adaptive immunity is especially important in populations with a high burden of iron deficiency.

Poster number: 31

Title:

Cellular iron deficiency impairs mast cell development and degranulation

Authors:

Hannah Murray, Dana Costigan, Maria Obregon Comino, Andrew Armitage, Shamsideen Yusuf, Giulia Pironaci, Alexandra Preston, Clare Hardman, Timothy Hinks, Hal Drakesmith

Departmental Affiliations:

MRC Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom

Abstract:

Iron deficiency and mutations that disable the transferrin receptor (TfrcY20H/Y20H) impair immune responses to infection and vaccination. How iron deprivation influences allergic responses, particularly mast cell biology, has been relatively unexplored. Given that iron is required for several enzymes involved in eicosanoid synthesis, we hypothesise that iron restriction may impair mast cell function and could influence the severity of allergic disease.

Mast cells were grown from murine bone marrow progenitors through in-vitro differentiation with IL-3 and SCF over 21 days. Degranulation was induced by sensitisation with anti-DNP-IgE followed by challenge with DNP-BSA. We compared mast cells grown from wild-type and TfrcY20H/Y20H mice, and used the iron chelator deferiprone to pharmacologically induce iron deprivation.

During in-vitro differentiation, CD71 expression is initially high but decreases as the mast cells mature. This suggests that mast cells may rely on iron acquired during this period to fuel degranulation rather than active uptake during degranulation. Accordingly, $Tfrc^{Y20H/Y20H}$ mast cells exhibited reduced degranulation, indicated by decreased β-hexosaminidase release and lower LAMP1 surface expression compared to wild-type. In addition, $Tfrc^{Y20H/Y20H}$ mast cells also displayed reduced side scatter and less β-hexosaminidase within their granules, suggesting defects in granule formation due inefficient iron acquisition and utilisation. Consistent with this, wild-type mast cells treated with deferiprone prior to activation showed impaired degranulation, which was counteracted by ferric ammonium citrate supplementation.

Iron availability is important for mast cell degranulation in-vitro. Mature mast cells rely on iron acquired during development, making them sensitive to iron availability during differentiation. Ongoing work will test whether iron deprivation can impair mast cell function in-vivo and will investigate the mechanism by which iron supports degranulation.

Poster number: 32

Title: Studying the Function and Expression of TIM-3 on Cytotoxic T-cells

Authors: Toby Whitehead, Jacky Foo, Joseph Clarke, Cristina Tormo-Garcia, Simon Davis, Sumana Sharma

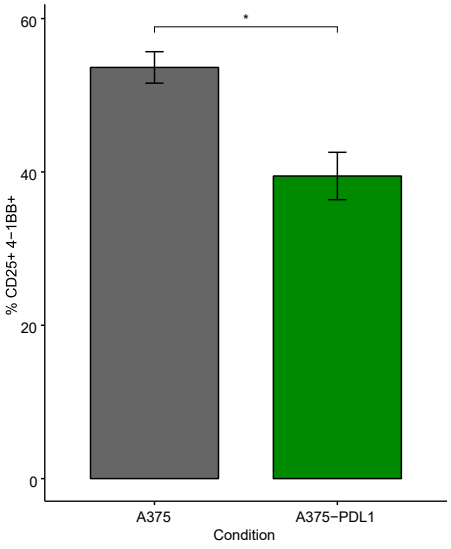
Departmental Affiliations: Weatherall Institute of Molecular Medicine, Radcliffe Dept. of Medicine, University of Oxford, OX3 9DS

Rationale

Checkpoint blockade immunotherapies targeting inhibitory receptors on cytotoxic T-cells have become a vital part of cancer treatment, but development of these drugs has outpaced knowledge of how the receptors function. This has created a clinical landscape where, despite the increasing number of approved checkpoint blockade drugs, treatment still fails in over half of patients. The inhibitory receptor TIM-3 is expressed on dysfunctional T-cells in cancer, making it a prime potential therapeutic target and creating a critical need to understand TIM-3 expression and function to guide development of effective treatements. **Methods**

We use both computational and wet lab techniques to study TIM-3. We study TIM-3 expression and regulation by analysing expression levels in an atlas of cytotoxic T-cells from cancer patients. We also use functional assays to measure T-cell activation. We engineer both immortal cell lines and human T-cells to express a chimeric PD-1–TIM-3 receptor, enabling TIM-3 activation through the PD-1/PD-L1 interaction. We can measure TIM-3 signalling effects on T-cell activation and function through killing of melanoma cells and expression of activation markers and cytokines. **Key Results**

We have identified TIM-3 as being expressed almost exclusively on 'exhausted' T-cells that have experienced chronic activation, particularly in metastatic tumours. In our experimental assays, we find that TIM-3 has a mild inhibitory effect on T-cell activation, cytotoxic function and cytokine release. This effect is unchanged when SHP-1 or SHP-2, phosphatases critical to PD-1 and BTLA function, are knocked out.



Activation of PD-1-TIM-3+ T-cells with & without PD-L1 binding

Conclusions

Together, these results indicate that targeting TIM-3 and reducing its function could at least partially restore function in 'exhausted' cytotoxic T-cells, demonstrating its potential as a target for checkpoint blockade therapies both by itself and in combination with other treatments. The finding that TIM-3 levels are higher in T-cells from metastatic tumour sites suggests a potential use in treatment of advanced cancers.

Poster number: 33

Title: **Exploring the Role of Arsenite-3-Methyl Transferase (As3mt) in Cardiometabolic Disease**

Authors: Yang Hu[1](Postdoc Fellow), Keith M. Channon[1]
Departmental affiliations:
[1] Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford.
RDM Research theme (please select a maximum of 3 and delete as appropriate):

- Cardiovascular Science
- Immunology and Infection
- Cellular and Molecular Biology

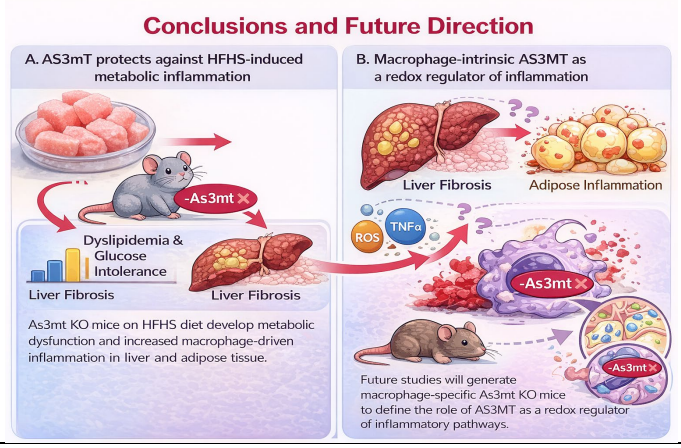
Arsenic-3-methyltransferase (AS3MT) is best known for its role in arsenic detoxification; however, recent genetic studies have linked AS3MT to cardiometabolic traits including obesity and atherosclerosis, suggesting broader functions beyond xenobiotic metabolism. Our previous work identified *As3mt* as a tetrahydrobiopterin (BH_4)-regulated redox gene[1,2], implicating it in the maintenance of cellular redox balance and adaptive responses to oxidative stress. Despite this, the role of *As3mt* in cardiometabolic homeostasis and inflammation remains poorly defined.

Here, we investigated whether *As3mt* functions as a redox regulator of macrophage-driven inflammation under metabolic stress. Using LacZ reporter mice, we found that *As3mt* is highly expressed in liver and adipose tissue and is further upregulated by high-fat, high-sugar (HFHS) feeding. LacZ-positive signal localized to crown-like structures in adipose tissue, and immunofluorescent staining showed colocalization of β-galactosidase with the macrophage marker CD68, confirming *As3mt* expression in adipose macrophages.

To define functional consequences, we performed 12-week HFHS diet studies using *As3mt*^{KO} mice. Compared to controls, As3mt-deficient mice exhibited modestly increased body weight, impaired glucose tolerance, and dyslipidemia, with elevated total cholesterol and LDL levels. Histological analysis revealed marked hepatic steatosis and fibrosis following HFHS feeding, which were significantly exacerbated in knockout mice. Adipose tissue inflammation was also increased, as evidenced by enhanced crown-like structure formation and macrophage infiltration, consistent with a pro-inflammatory macrophage phenotype.

Together, these findings identify *As3mt* as a BH_4-regulated redox modulator of macrophage inflammatory activation that protects against diet-induced metabolic dysfunction. Ongoing studies using macrophage-specific *As3mt* knockout models will further define the mechanistic role of *As3mt* in cardiometabolic disease.

[1] McNeill E, Crabtree MJ, Sahgal N, et al. Regulation of iNOS function and cellular redox state by macrophage Gch1 reveals specific requirements for tetrahydrobiopterin in NRF2 activation. Free Radic Biol Med. 2015;79:206-216.
[2] Douglas G, Hale AB, Patel J, et al. Roles for endothelial cell and macrophage Gch1 and tetrahydrobiopterin in atherosclerosis progression. Cardiovasc Res. 2018;114:1385-1399.



Poster number: 34

TITLE: Stroke-specific early warning score improves the prediction of deterioration for stroke patients in hospital: a retrospective cohort study.

AUTHORS: **James Garrard**[1] (Doctor of Medicine Student), Stephen Gerry[2], David Eyre[3], James Kennedy[1]

AFFILIATIONS: [1]Investigative Medicine Department, Radcliffe Department of Medicine, University of Oxford, UK
[2]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford
[3]Big Data Institute, Nuffield Department of Population Health, University of Oxford, Oxford, UK

ABSTRACT:

Research rationale

The use of the National Early Warning Score (NEWS2) is mandated to identify in-patients at risk of clinical deterioration. Derived from mixed in-patient populations, NEWS2 may not be appropriate for use on an Acute Stroke Unit. For instance, false positive alerts are likely due to the physiological response to acute stroke triggering the NEWS2 thresholds as opposed to necessarily being associated with deterioration. A stroke-specific EWS (StrEWS) may improve the use of limited clinical resources.

Aims

1) Compare the accuracy of NEWS2 and a recalibrated StrEWS to predict deterioration
2) Identify specific groups of stroke patients at increased risk of deterioration

Methodology

Clinical observations from the Electronic Healthcare Records from consecutive acute stroke admissions to the Oxford Acute Stroke Unit were extracted from the Infections in Oxfordshire Research Database (19/SC/0403, 19/CAG/0144) into derivation (July 2020 – August 2023; N=2358) and validation (September 2023 – September 2024; N=763) cohorts. StrEWS was recalibrated using a centile-based approach[1] within the derivation cohort. The accuracy of NEWS2 and StrEWS were compared to predict deterioration (defined as either a drop in Glasgow Coma Scale ≥2 from presentation, or death). Adjusted Cox proportional hazards models compared deterioration across differing stroke types and treatments.

Results

Data from 3121 patients [median age=77(65-85), 45% female] comprising 86822 observation sets were analysed. StrEWS improved the prediction of deterioration in both derivation and validation cohorts (AUC 0.70 vs 0.54, and 0.72 vs 0.56, respectively). After adjustment, patients with haemorrhagic stroke and following thrombectomy had the highest deterioration rates.

Conclusions

A stroke-specific EWS improves identification of in-patients on an Acute Stroke Unit at risk of deterioration, with 17 more patients identified per 100 admissions than NEWS2. Next steps include understanding if incorporating routinely available imaging data can improve this further, and external validation.

Graphical abstract figure

1. Tarrasenko et al. Resuscitation 82 (2011) 1013– 1018.

Poster number: 35

Statistical methods for split-sample laboratory studies: observations from a systematic review of irradiated platelets

Josie Sandercock, Louise Geneen, Lorna Cain, Michael Wiltshire, Sue Proffitt, Catherine Kimber, Carolyn Dorée, Susan Brunskill, Lise Estcourt

Aims

In a systematic review of irradiated platelets we included *in vitro* studies which used split (paired) samples. Paired samples provide a much more powerful design than randomisation because the groups are identical at baseline and the difference between pairs can be analysed directly.

Methods

For each included study we checked statistical methods sections and reporting of results to establish whether the data had been analysed as pairs or independent groups, and whether numerical results (for pairs or groups) could be extracted for meta-analysis.

Results

We included 43 in-vitro studies; 33 full-text, 10 abstract-only.

14 (33%) used paired analysis but only one reported enough numerical information for meta-analysis.

25 (58%) reported enough information to be included in a meta-analysis of the difference between groups instead of between pairs.

For the sole study which reported its paired analyses in enough detail to reconstruct, the 95%CI for the difference between groups was, depending on the outcome, between 1.4 and 17 times wider than the 95%CI for the difference between pairs, implying effective sample sizes of between 2 and 291 times larger when analysed as pairs.

Discussion

Analysing groups instead of pairs does not introduce bias but does inflate the standard error.

Paired (split) samples are a powerful tool for *in vitro* studies, maximising the information available for any given sample size. Researchers should analyse the difference between pairs (not groups) and report enough information to allow calculation of the SE of the mean difference between pairs (eg p-value, CI, SD, or SE).

Poster number: 36

Title

Divergent Functional Consequences of Different *TTN* Truncating Variants in Dilated Cardiomyopathy

Authors

Rosemary B. Kirk[1], Alexander Sparrow[1], Christopher Toepfer[1], Hugh Watkins[1]

Departmental affiliations

[1]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, United Kingdom

Abstract

Research rationale

Familial dilated cardiomyopathy (DCM) is a common and harmful condition. The leading genetic cause is heterozygous truncating mutations in *TTN*, which encodes titin, the largest protein in the human body. However, it remains unclear how *TTN* variants drive disease, with evidence for both dominant negative mechanisms and haploinsufficiency. Further, the effect of variant location within *TTN* has not been elucidated; most research focuses on distal A-band variants with minimal exploration of proximal I-band variants. Understanding how different *TTN* variants disrupt cardiomyocyte function is essential for the development of gene-based therapies for familial DCM.

Methodology

We used CRISPR-Cas9 gene-editing to generate human induced pluripotent stem cell (hiPSC) lines carrying disease-causing heterozygous truncating mutations in either the I-band or A-band of *TTN*. These were differentiated into hiPSC-derived cardiomyocytes (hiPSC-CMs) for phenotypic analysis. We assayed *TTN* mRNA and titin protein levels, as well as functional outputs including metabolism, contractility, action potentials, and calcium transients.

Results

Both I-band variants and A-band truncating variants resulted in reduced full-length titin and a persistent truncated product. Both variants displayed reduced contractility, consistent with a DCM phenotype. Despite these similarities in insult and disease phenotype, other parameters differed between the cell lines. The A-band variant caused prolonged calcium transients and action potentials compared to wildtype controls, while in the I-band variant these were faster. The I-band variant also caused more severe metabolic perturbations.

Conclusions

These hiPSC-CM models showed that truncating mutations in different regions of *TTN* can lead to a shared DCM phenotype through distinct disease mechanisms, informing the design and application of therapeutic strategies.

Poster number: 37

Title: The synaptic glycoprotein CBLN4 acts as a paracrine messenger controlling insulin and glucagon secretion in pancreatic islets

Authors: Sarah L Armour[1], Ildem Akerman[2],and David J Hodson[1]

Affiliations: [1]OCDEM, Radcliffe Department of Medicine, University of Oxford, UK; [2]Department of Metabolism and Systems Science, University of Birmingham, Birmingham, UK.

Abstract:

Intro: Somatostatin, secreted by pancreatic delta cells, contributes to the regulation of blood glucose levels by repressing both insulin and glucagon secretion. Altered somatostatin secretion is associated with glucose intolerance and defective counter-regulatory responses to hypoglycaemia. Despite this, there are no known functional delta cell markers. We therefore sought to identify cell-type–specific genes associated with somatostatin expression.

Methods: Published scRNA-seq/ATAC-seq datasets[1-3] were used for genomic analyses, followed by confirmation of protein expression in isolated mouse and human islets. Lentivirus-mediated knockdown was used to reduce gene expression, followed by hormone secretion assays, as well as FRET-based cAMP imaging.

Results: Analysis of genomic datasets from brain and pancreas identified Cerebellin 4 (CBLN4) as a shared marker of delta cells and somatostatinergic interneurons in both mouse and human. CBLN4 is located within a gene desert with few associated chromatin marks, consistent with highly cell-type–specific expression in somatostatin-positive cells. CBLN4 is a synaptic glycoprotein with roles in long-term potentiation and the organisation of inhibitory GABAergic synapses. Delta cells express high levels of CBLN4 protein, with low-to-moderate expression in alpha cells. CBLN4 knockdown increased somatostatin secretion at high glucose. Both glucagon and insulin secretion were impaired under the respective stimulatory conditions following CBLN4 knockdown. This was accompanied by a reduction in intracellular cAMP levels, suggesting Cbln4 signals upstream of cAMP-dependent pathways.

Conclusion: CBLN4 plays an important role in paracrine signalling between glucose-regulating hormones within the islet. Alterations in CBLN4 expression or glycosylation may therefore contribute to dysregulated insulin and glucagon secretion in diabetes.

References:

1. Mawla AM, Huising MO. Navigating the Depths and Avoiding the Shallows of Pancreatic Islet Cell Transcriptomes. *Diabetes*. 2019 Jul;68(7):1380-1393.
2. Balboa, D., Barsby, T., Lithovius, V. *et al.* Functional, metabolic and transcriptional maturation of human pancreatic islets derived from stem cells. *Nat Biotechnol* 40, 1042–1055 (2022).
3. Tabula Muris Consortium et al. Single-cell transcriptomics of 20 mouse organs creates a Tabula Muris. *Nature* vol. 562,7727 (2018): 367-372

Poster number: 38

Title: **Characterizing *GLP1R*/GLP1R expression in human iPSC-derived pancreatic islets (SC-islets) for cell therapy applications**

Authors: Ali H. Shilleh[1,2], Christopher Carlein[1], Imogen L Rayer[1], Claire Bristow[1], Charlotte Clinton[1], Malgorzata Cyranka[2], Remi Fiancette[3], Katrina Viloria[1], Amanda Oakie[5], Alexey Epanchintsev[2], Jason Tong[1], Maria Christina Nostro[5], Johannes Broichhagen[4], Ildem Akerman[3], Carina Ämmälä[2], David J. Hodson[1]

Departmental affiliations:
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[2] Novo Nordisk Research Center Oxford (NNRCO), United Kingdom
[3] Institute of Metabolism and Systems Research (IMSR), University of Birmingham, United Kingdom
[4] Leibniz-Forschungsinstitut für Molekulare Pharmakologie Berlin, Germany
[5] McEwen Stem Cell Institute, University Health Network, Canada

Abstract:
Research rationale: Pancreatic beta cells regulate blood glucose levels by the secretion of insulin. Rodent studies have established GLP1R as a beta cell-specific marker essential for beta cell maturation and function. However, its expression and role in human beta cells remain poorly characterized due to limited patient sample availability and the lack of validated detection tools. To address this, we employed induced pluripotent stem cell-derived islets (SC-islets) as a robust model to investigate human endogenous GLP1R expression and activity.

Methodology: SC-islets were generated using a 5-week maturation protocol. GLP1R expression was quantified using the fluorescent GLP1R antagonist LUXendin645. Glucose-stimulated insulin secretion was assessed, while beta cell maturation markers were analyzed via RNA sequencing and flow cytometry. cAMP production was monitored using an $EPAC^{VV}$-based FRET sensor, and metabolic activity was evaluated via ATP/ADP ratio using a Perceval HR biosensor and Seahorse assays.

Results: We generated SC-islets consisting of 60% monohormonal insulin-positive cells. LUXendin645 labeling confirmed GLP1R protein expression in 50% of SC-islets, consistent with published scRNA-seq data.[1] FAC-sorted $GLP1R^{+}$ SC-islets exhibited higher expression of beta cell maturity and mitochondrial markers. As SC-islets undergo maturation, activation of GLP1R by Exendin-4 (agonist): (1) induced robust cAMP responses, (2) stimulated static and dynamic insulin secretion, and (3) increased cytosolic ATP/ADP ratios. While SC-islets lacking GLP1R expression showed impaired beta cell functionality.

Conclusions: We demonstrate that SC-islets express functional GLP1R at transcript and protein levels. GLP1R serves as a reliable surface marker for identifying mature, functional SC-islets. Future studies will determine functional robustness comparing GLP1R-enriched and GLP1R KO SC-islets. This will provide a foundation for refining SC-islet selection for transplantation purposes and promoting SC-islets as a human disease-relevant model for the investigation of GLP1R signaling.

References:

1. Balboa, D., Barsby, T., Lithovius, V. *et al.* Functional, metabolic and transcriptional maturation of human pancreatic islets derived from stem cells. *Nat Biotechnol* 40, 1042–1055 (2022).

Poster number: 39

Title: ITGBP4 at the nexus between mechanotransduction and post-transcriptional regulation

Authors:
Jackson White[†, §]
Vedanta Mehta [†]
Daniel Castranova [§]
Brant M. Weinstein [§]
John Reader [†]
Ellie Tzima [†]
NOTE: Presenting Author, Jackson White, is a DPhil student.

Departmental Affiliations:

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[§] Section on Vertebrate Organogenesis, National Institute of Childhood Health and Human Development, USA

Abstract:

Mechanical forces from flowing blood within the vasculature are major regulators of blood vessel development and homeostasis via regulation of gene expression of endothelial cells (ECs). Recent findings have reported a role for epigenetics, including DNA methylation and histone modification, in regulating gene expression in response to mechanical stimulation of ECs [1, 2, 3]. However, the underlying regulatory mechanisms that govern accessibility of DNA during mechanical stimulation haven't been thoroughly explored. Our lab has recently shown that integrin beta 4 binding protein (ITGBP4), also known as eukaryotic initiation factor 6, regulates mechanical responses in endothelial cells 4 . ITGBP4, known pre-eminently as a ribosomal chaperone with a role in ribosomal biogenesis, has also been shown to be involved in RNA interference via its association with microRNA processing machinery 5 . RNA interference also occurs in the nucleus by the RNAinduced transcriptional silencing (RITS) complex, which governs chromatin accessibility. I hypothesize that ITGBP4 serves as a regulatory conduit between mechanical cues, like fluid shear stress from flowing blood in the vasculature, and gene expression, regulated by the RITS complex. Here, we share evidence of a direct interaction between ITGBP4 and a constituent member of the RITS complex, AGO2, their flow-dependent association *in cellulo*, and changes in histone methylation. Using the experimentally accessible zebrafish (*Danio rerio*), we reveal ITGBP4- specific developmental and vascular phenotypes in vivo and show RNA sequencing data linking ITGBP4 to the regulation of DNA ultra-structure in endothelial cells.

References

1. Chen et al., Proceedings of the National Academy of Sciences, 2025

2. Hu et al., Stem Cells International, 2022

3. Danielsson et al., Molecular Biology of the Cell, 2022

4. Keen et al., Journal of Cell Biology, 2022

5. Chendrimada et al., Nature, 2007

Poster number: 40

Assessing risk of bias for in vitro studies of split (paired) samples included in a systematic review of irradiated platelets

Louise J Geneen, Lorna Cain, Mike Wiltshire, Sue Proffitt, Catherine Kimber, Josie Sandercock, Carolyn Dorée, Susan J Brunskill, Lise J Estcourt

Aims

To assess the risk of bias (ROB) of the *in vitro* studies included in a systematic review of irradiated platelets. There are many tools available for assessing ROB in clinical trials but we could not find an equivalent instrument for *in vitro* studies.

Methods

We adapted an existing ROB tool to suit in vitro studies using the domain headings of the original Cochrane ROB tool and compare the two below

Domain	Cochrane ROB tool	Our new ROB tool for in-vitro paired studies
Selection bias	• Random sequence generation • Allocation concealment	Inclusion of only paired samples covers issues around baseline differences that randomisation is designed to overcome.
Performance bias	• Blinding of participants • Blinding of personnel	Storage and handling of split packs (includes blinding of handlers, or use of simultaneous handling)
Detection bias	Blinding of outcome assessors	• Handling of samples during testing • Random outcome assessment (order of testing, timing) • Blinding of outcome assessors • Measuring the outcomes (validated analysers/methods, same methods used across samples)
Attrition bias	Incomplete outcome data	Same as Cochrane ROB: excluded samples, reasons for attrition/loss of samples
Reporting bias	Selective outcome reporting	Same as Cochrane ROB: protocol publication, planned outcomes reported, and unplanned outcomes
Other biases	Any other biases (often funding, conflicts, baseline imbalances)	Same as Cochrane ROB: any other biases (manufacturer/pharmaceutical sponsorship, conflicts, unusual statistical analysis)

Conclusions

We have developed and used a ROB tool suitable for use in paired sample in-vitro studies that is simple to use, and includes assessment of all domains laid out by Cochrane.

Poster number: 41

Does irradiation affect the quality, effectiveness, and safety of platelets for transfusion? A systematic review

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Aims

To identify any detrimental effects of irradiation on platelet quality and clinical effectiveness.

Methods

We included RCTs and split-sample laboratory studies. We followed PRISMA guidelines and pre-registered the protocol on PROSPERO [CRD42023441930].

Results

We found 44 eligible studies: 41 *in vitro*, two RCTs in healthy volunteers which included *in vitro* results, one RCT in thrombocytopenic patients. X-ray was used exclusively in three studies, and alongside gamma irradiation in one study. Two studies did not report the source of irradiation. The remaining 38 studies used gamma irradiation only. We found:

- Strong evidence of a small decrease in pH (day 7) with irradiation: MD -0.04 (−0.07 to −0.00)
- Some evidence of an increase in P-selectin (day 5) with irradiation: MD 1.58% (0.72-2.45). No difference in supernatant glucose (days 5 and 7) and P-selectin (day 7).
- Very weak evidence of a difference in pH (day 5), and of no difference in post-transfusion bleeding risk (WHO 2+) or post-transfusion platelet survival time.

Conclusions

Where there is some evidence of detriment from irradiation, differences are small *in vitro*, and are unlikely to affect clinical outcomes following transfusion. However, the evidence base is limited. Only half the included studies could be included in any analysis. There is very limited evidence for x-ray as a source of irradiation and, given the potential benefits of using x-ray over gamma irradiation (ease of use and safety requirements), we would welcome further research comparing x-ray to gamma, and x-ray to a non-irradiated control.

Poster number: 42

Developing an integrated cardiac magnetic resonance and cardiopulmonary exercise testing platform to characterise exercise intolerance

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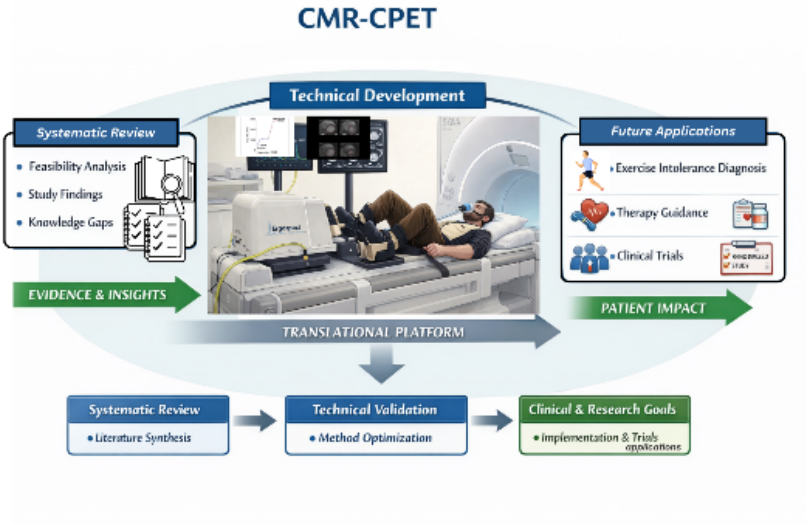
Rationale: Exercise intolerance and breathlessness are highly prevalent symptoms with multifactorial origins involving cardiac, pulmonary, haematological, and skeletal muscle systems. Conventional cardiopulmonary exercise testing (CPET) quantifies peak oxygen uptake ($\dot{V}O_2$) but cannot localise the dominant physiological limitation. Invasive CPET can resolve this limitation but is restricted to specialist centres. A non-invasive, integrative approach capable of interrogating the oxygen cascade within a single assessment is therefore needed. **Methods:** We undertook a structured programme of preparatory work to enable future simultaneous cardiac magnetic resonance–cardiopulmonary exercise testing (CMR-CPET). This comprised (1) a systematic review of all published studies performing true simultaneous CMR-CPET to define feasibility, technical approaches, and physiological insights; (2) local technical development focused on adapting respiratory gas analysis for use within the MRI environment; and (3) protocol design integrating real-time exercise CMR, respiratory gas exchange, arterial oxygen content measurement, and complementary skeletal muscle imaging (^{31}P-MRS and arterial spin labelling). Together, these elements will permit non-invasive decomposition of $\dot{V}O_2$ into cardiac output and peripheral oxygen extraction during exercise. **Results:** The systematic review identified a small but consistent body of evidence demonstrating the feasibility and safety of simultaneous CMR-CPET (See figure 1), with reproducible physiological patterns across health and disease. Locally, technical validation confirmed reliable gas-exchange measurement during supine exercise with extended tubing, and robust real-time cardiac imaging during exercise. These steps establish readiness for first-in-study combined CMR-CPET acquisition. **Conclusions:** This work lays the methodological foundation for a fully integrated, non-invasive CMR-CPET platform. By enabling interrogation of the oxygen cascade from pulmonary uptake to peripheral utilisation, this approach has the potential to transform the mechanistic assessment of exercise intolerance and support physiology-guided diagnosis and intervention.

Figure 1. CMR-CPET platform.



Poster number: 43

Analysing hypertensive multi-organ damage across different ethnic groups in the UK Biobank

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Abstract

Elevated blood pressure (Hypertension) is a major cause of cardiovascular disease-related deaths, affects approximately 1.3 billion people worldwide and is a major contributor to cardiovascular, cerebrovascular, and renal disease. Long-term hypertension results in structural and functional changes in multiple organs including the heart, brain, kidney and vasculature. These have been meticulously mapped, using over 500 markers in the novel machine learning approach: HyTwin model. The model is based on imaging and non-imaging data from over 27,099 UK Biobank participants and gives a global organ damage score (*HyperScore*) as well as distinct disease phenotypes knowns as HyperTrajectories which allow further characterisation of the organ damage.

This study aims to assess the applicability of the HyTwin model in different ethnic populations in the UK Biobank and participants of the Atherosclerosis Risk in Communities (ARIC) study.

We find no significant differences in the HyperScore amongst five categorised ethnic groups (African, Asian, British, Chinese and Other) but report significantly higher HyperScores in males across all ethnicities, indicative of higher organ damage in men compared to women. Differences in HyperTrajectory phenotypes are also pronounced in some ethnicities, with African females having higher odds of being in Trajectory 1 (Cardiac) while the Asian population as whole had significantly higher chance of being in Trajectory 2 (Lipoprotein). These results show a need to consider gender specific and possibly ethnic specific clinical approaches for managing hypertension.