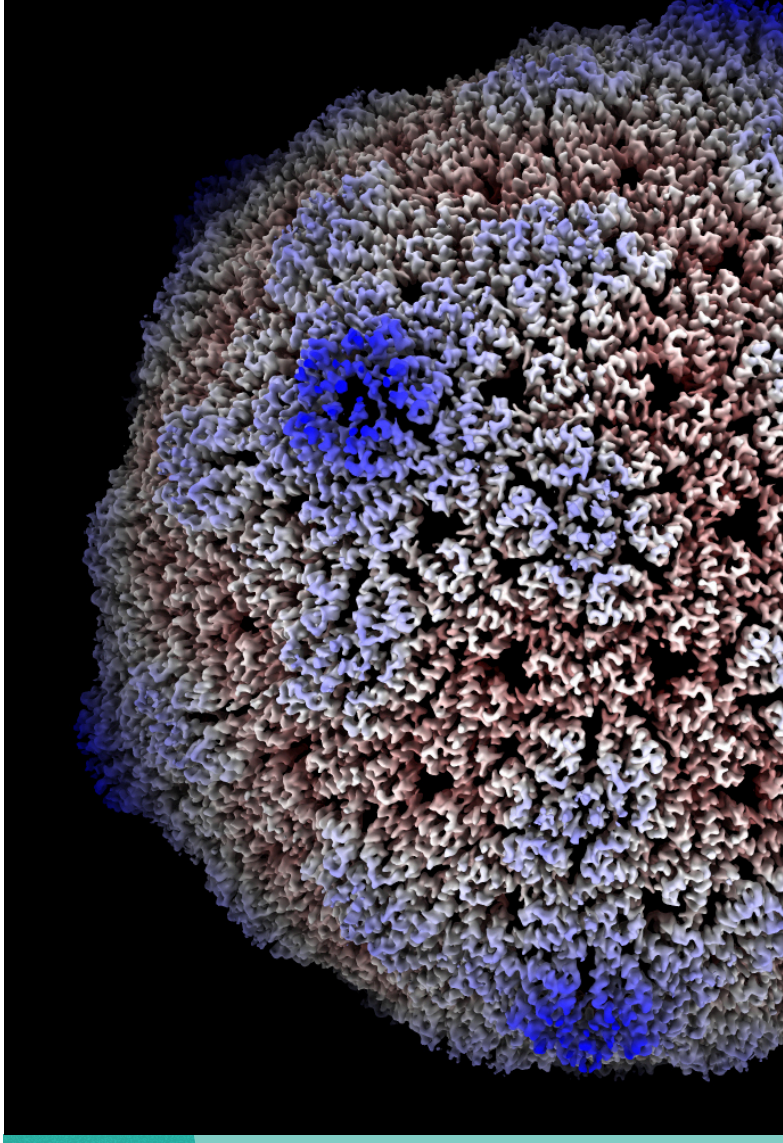
UNIVERSITY OF CAMBRIDGE | Department of Medicine



Annual Research Day

19 September 2025

med.cam.ac.uk

Programme

Friday 19 September

Welcome to our 2025 Annual Research Day

Our Annual Research Day is the largest forum for presenting research by faculty, staff, and trainees in the Department of Medicine.

Research Day showcases the investigative strengths of each section, shining a spotlight on the research that enriches and elevates our community.

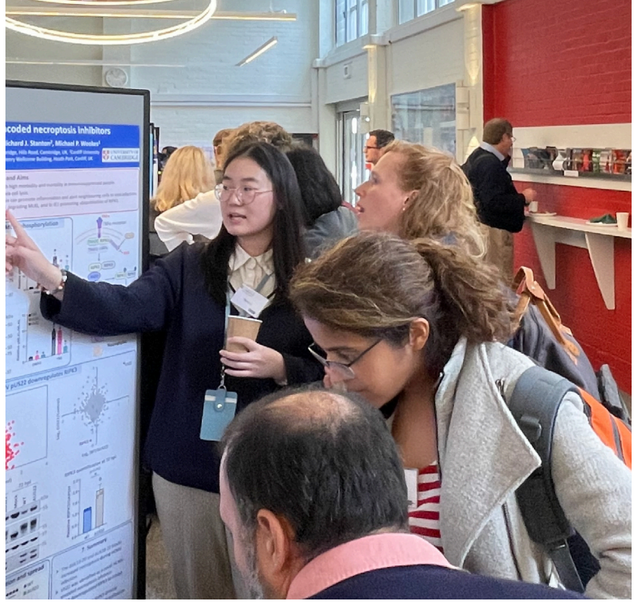
It's also a day of connection — among researchers, between mentors and mentees, and between leadership and the adventurous minds that drive the discovery community.

This year, we are honoured to welcome Keynote Speaker Sarah Teichman, PhD, Chair of Stem Cell Medicine at the University of Cambridge and Director of EnsoCell Therapeutics.

Once again, we're thrilled that the keynote address, research talks, and award presentations will take place alongside a vibrant poster session, illustrating the bold and creative initiatives that define our department.

This event promises to foster meaningful collaborations while continuing to leverage the investigative excellence embedded across all sections.

Poster presentations from last year ►



Annual Research Day 2025

Agenda

Dining Hall	**Registration on the Dining Hall Balcony** Welcome refreshments & Danish pastries	08:30
Main Auditorium	**Welcome** Duncan Richards (Head of Department)	09:00

Session 1

Lead: Virginia Pedicord

Main Auditorium	**Eoin McKinney** When and how does T1D start? characterizing early antigen-specific autoimmunity at single cell level	09:15
	Delphine Cuchet-Lourenco Regnase-1 deficiency: VCAM1-expressing T cells and a new mechanism of IFNγ regulation implicated in autoimmunity	09:30
	Joe Joiner Molecular basis of autoimmune disease protection by MDA5 variants	09:45
	Maire Roder Neutrophils undergo a phenotypic switch following extended pathogen exposure	10:00
Dining Hall	*Refreshment break*	10:15

Session 2: Keynote and Guest Speakers

Lead: Duncan Richards

Main Auditorium	**Keynote: Sarah Teichman** 'Translating the Human Atlas'	10:40
	Hana Lango Allen Healthcare Data Research Infrastructure	11:40
Dining Hall	**Lunch and posters**	12:00
Dining Hall	**Poster Judging starts**	12:30
Main Auditorium	**Flash Talks**	13:00

Agenda

Session 3

Lead: Andrew Conway-Morris

Main Auditorium

Dennis Wang Oral vaccination with engineered bacteria induces CNS-protective T cells against meningitis	14:00
Leah Hurst Characterising tight junctions in the human airway epithelium in health and disease	14:15
Daniel Whitehouse Head Injury and its Impact on Neurodegeneration, Cognition, and Brain Structure: Evidence from the UK Biobank	14:30
Emmanuel Stamatakis Acute Thalamic MRI Markers of Chronic Post-Concussive Symptoms	14:45
Eckhart De Bie The survival discrepancy between Pulmonary Arterial Hypertension patients eligible for clinical trials and clinical reality	15:00
Rowena Jones StratosPHere 1 Study: a novel BMP target engagement biomarker panel for use in clinical trials in PAH	15:10
Refreshment break (Dining Hall)	15:35

Session 4

Lead: Matthew Hoare

Main Auditorium

Ayden Case Preliminary results from the Ellipse trial (Low-dose Interleukin-2 on the Immune Landscape of Human Atherosclerotic Plaques at Single Cell Resolution)	16:00
Tetsuo Hasegawa 3D imaging of the synovium defines an intricate immunological defence system at the blood-joint barrier	16:15
David Thomas A crucial role for thyroid hormone signalling in Natural Killer Cell Biology	16:30
Emma Hodson The role of hypoxia and HIF signalling in sympathoadrenal development	16:45
Prizes & Close	17:00

*Please note that photography, filming and/pr sound recording will be taking place during this event and may be used for promotional purposes.

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Keynote Speaker

Sarah Teichmann

Chair, Stem Cell Medicine
Director, EnsoCell Therapeutics
Department of Medicine, Cambridge

> *The Human Cell Atlas is a project to map the cell types in the human body in terms of their complete molecular fingerprint.*

Translating the Human Atlas

Sarah completed her PhD at the MRC Laboratory of Molecular Biology in Cambridge, UK, and as Beit Memorial Fellow at University College London.

She established her research group at the MRC Laboratory of Molecular Biology in 2001, where her main discoveries included the finding that protein assembly pathways are stereotypical and conserved.

In 2013, she transitioned to the Wellcome Genome Campus, where she became the first and, to date, the only faculty member appointed across both the EMBL-European Bioinformatics Institute and the Wellcome Sanger Institute.

In 2016, she was appointed as the Head of the Cellular Genetics programme at the Wellcome Sanger Institute and co-founded the Human Cell Atlas initiative.

From April 2024, she was appointed chair in Stem Cell Medicine at the University of Cambridge, within the Department of Medicine and the Cambridge Stem Cell Institute. Additionally, Sarah dedicates part of her time to GlaxoSmithKline and to EnsoCell Therapeutics, the startup company she co-founded.

The Teichmann lab focuses on developing and applying cell atlas technologies to understand human tissue architecture, particularly examining how cellular diversity is generated in the immune system and during development.

Current members of the Teichmann Lab
Source: https://www.teichlab.org/

Human Cell Atlas: Co-founder & Co-lead

Sarah Teichmann is one of the co-founders of the Human Cell Atlas (HCA), a global consortium that is mapping every cell type in the human body, creating a 3-dimensional Atlas of human cells to transform our understanding of biology and disease.

The Teichmann Lab is one of the leading groups in the Human Cell Atlas project, studying the composition of many human tissues in both healthy and disease states using single cell and spatial genomics, coupled with computational analyses.

HCA's mission

To create comprehensive reference maps of all human cells—the fundamental units of life—as a basis for both understanding human health and diagnosing, monitoring, and treating disease.

HUMAN CELL ATLAS

Annual Research Day 2025

Guest Speaker

Hana Lango Allen

Head of Data Strategy and Partnerships
Cambridge University Health Partners

"The exchange of scientific ideas was pivotal to many advances."

Healthcare Data Research Infrastructure

Hana joined CUHP in 2024 as the Head of Data Strategy and Partnerships.

She works closely with Health Informatics Team at Health Innovation East, with particular focus on developing research-enabling healthcare data infrastructure and data assets that meet broad range of requirements across healthcare, academic and industry partners.

Previously, Hana was the Scientific Director at NHS East Genomic Laboratory Hub, where she provided scientific and strategic leadership on diagnostic tests, R&D activities, collaborative projects and research partnerships with clinicians and industry.

She has subject matter expertise in genomics and bioinformatics applied to human traits and diseases, developed over a 15-year research career at the universities of Leicester, Exeter and Cambridge.

Hana is keen supporter of talent development, and teaches at the University of Cambridge MPhil in Population Health Sciences.

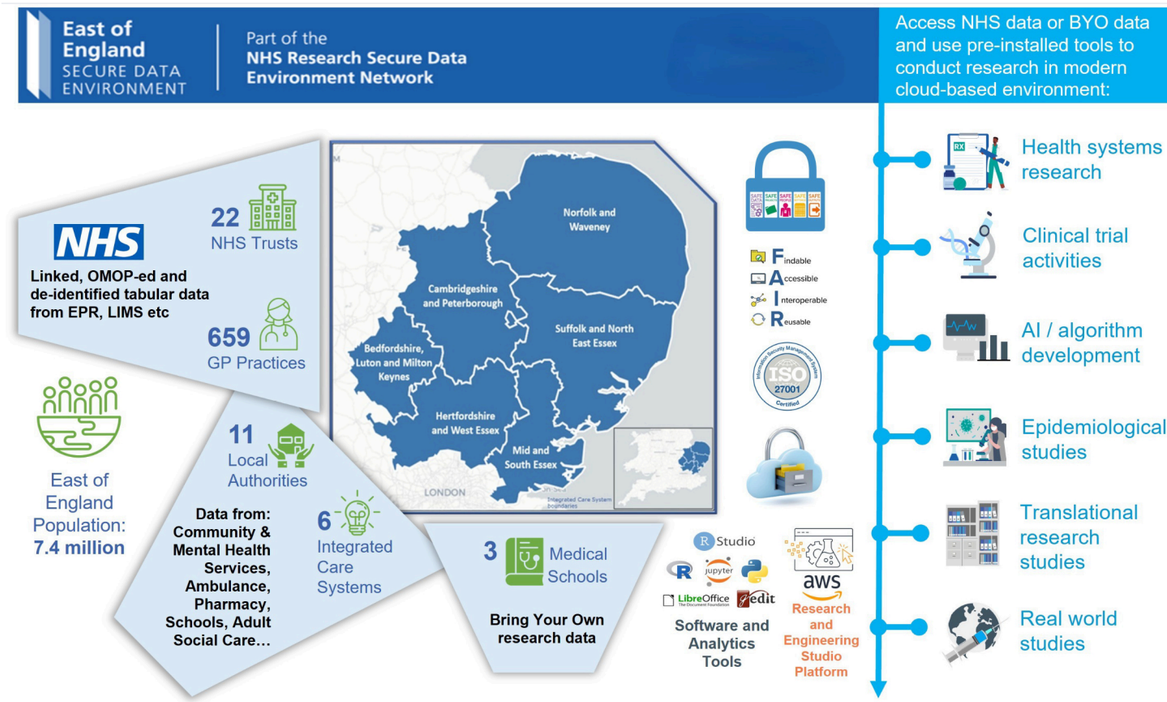
Healthcare Data Research Infrastructure: focus on East of England SDE

There is a range of data and digital infrastructure available in the Cambridge ecosystem for healthcare data research, but when it comes to analysing routine NHS data it is not always clear which platform to use, under which governance arrangements, and what support services are available.

The East of England SDE

Research SDE Network, is becoming the default platform for querying and analysing linked and deidentified NHS data from single or multiple data providers in the region, with already established governance and legal approvals, end-to-end user journey including training and technical support, as well as contracting and pricing models. The EoE SDE also supports "Bring Your Own Data" projects, allows for multi-institutional collaborations and commercial arrangements, has AI security tools, and can be used to securely link research studies with NHS data.

The platform is hosted by Cambridge University Hospitals, with the operational delivery and support provided by the Health Informatics team at Health Innovation East.



Short talk abstracts: Session 1

Unpicking autoimmunity, cell by cell, before it starts

Eoin McKinney, Kasra Bahadori, Dan Griffiths, The TEDDY consortium

Background

Type 1 diabetes (T1D) is a prototypical chronic autoimmune disease characterised by T cell mediated destruction of insulin-producing pancreatic islet cells. The mechanisms driving onset and progression of islet autoimmunity (IA) in some but not others remain unknown.

The Environmental Determinants of Diabetes in the Young (TEDDY) study is a longitudinal, multi-center research project that investigates environmental factors contributing to T1D in children at high genetic risk. TEDDY established a prospective cohort of 15,000 children followed 3-6 monthly from birth for 15 years at six clinical centres across four countries. Longitudinal collection of samples from at-risk individuals in TEDDY created the unique opportunity to characterize immune changes occurring prior to, during and after the onset of autoimmunity.

In a nested case:control design, we use peripheral blood of children who subsequently develop IA or T1D to perform multi-omic characterization of ~800,000 cells pre-enriched from12 immune cell subsets in n=60 samples spanning each of 3 disease 'windows' (prior to, during and after the onset of islet-reactive autoimmunity). Including sequence-tagged islet autoreactive CD8T cells facilitates detection, and detailed characterisation, of antigen-specific autoimmunity long before the onset of disease or other features of IA.

Summary

Here, we create a detailed multi-omic atlas of the development of T1D in 3 developmental windows: before (w1), during (w2) and after development of islet autoimmunity (w3). We apply unsupervised differential abundance (DA) analysis to scRNAseq data from each of 12 pre-enriched immune cell subsets (CD8Tmem, islet-specific CD8Tmem, CD4Tmem, CD4TmemReg, NK, Bmem, Plasmablast, CD16+monocytes, CD14+monocytes, cDC, pDC, DNT), identifying both the presence of disease-specific cell populations and the timing of their emergence.

We identify islet reactive (IA2Dex+) CD8Tmem cells >1 year before development of islet autoantibodies, showing they are more abundant and clonally expanded in cases compared to controls. Expanded, autoreactive CD8Tmem are enriched within a larger subset of DA cells showing altered pseudotime differentiation characterized by heightened interferon (IFN), interleukin-12 and antigen-receptor (AgR) signalling and by concurrently suppressed TNF signalling. Comparing autoreactive cells in cases with the smaller population seen in controls, we find the same pattern of skewed differentiation along with a lack of clonal expansion. Using extended mapping of VDJ TCR motifs, we identify pathogen-specific CD8Tmem responses and show that a similar shift in differentiation is apparent across multiple responses including CMV, EBV, influenza and in other autoreactive clones. Together, these data suggest that autoimmunity in T1D involves a pervasive shift in immune reactivity rather than development of a single aberrant, autoreactive clone.

Extending our analysis into the remaining 10 populations and show that a comparable pattern of skewed differentiation exists in each resulting in a consistent transcriptional signature differentiating case and control. By mapping these changes onto each disease timepoint we show that, while similarly skewed differentiation characterises cases in each cell type tested, changes emerge in different cell types at different timepoints. While observed changes are remarkably consistent between established T1D endotypes (defined by pattern of seroconversion), their timing of onset differs.

Conclusion

Together, our data demonstrate antigen-specific islet T cell autoimmunity long before other evidence of disease is detectable. We show that cases are marked by expanded autoreactive cells with altered differentiation characterised by enhanced IL12, IFN and AgR signalling and a specific suppression of TNF signalling. These changes are conserved not only in non-autoreactive clones but across every cell type tested suggesting that pervasive skew in immune cell signalling and differentiation promote autoimmunity and alter pathogen specific responses concurrently.

Our data inform the mechanisms of autoimmunity and therapeutic target selection at the earliest stages of T1D.

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Regnase-1 deficiency: VCAM1-expressing T cells and a new mechanism of IFNγ regulation implicated in autoimmunity

Delphine Cuchet-Lourenco, Matilde I. Conte, Sooyeon Chang, Nika Ten, Davide Eletto, Olivier Papapietro, Vincent Plagnol, Mike de Kok, Ilie Hashim, Lourdes Ceron-Gutierrez, Marlous van den Braber, James Curtis, Harriet C. T. Groom, Mailis Maes, Rainer Doffinger, Juan Garcia Vallejo, Cecilia Dominguez Conde, Joao Farela Neves, Sergey Nejentsev

Background

Autoimmunity develops as a result of a breakdown in immune tolerance and activation of autoreactive immune cells. Most of the common autoimmune diseases are polygenic suggesting dysregulation in multiple signalling pathways. By contrast, in monogenic Inborn Errors of Immunity (IEI), which also can result in autoimmunity, the disease is triggered by a single genetic defect. Therefore, the discovery of causative mutations in IEI allows tracing the molecular mechanisms leading to autoimmunity in humans from a defect in the function of a specific gene to patients' clinical and immunological phenotype.

Summary

Recently, we discovered the first patient with systemic autoimmunity caused by a homozygous protein truncating mutation in gene *ZC3H12A* leading to Regnase-1 deficiency. Regnase-1 is a regulatory RNase known to cut 3'UTRs of mRNAs of several pro-inflammatory genes leading to their degradation and therefore reduced protein expression, which restrains inflammation. In our patient, flow cytometry, bulk T cell transcriptome analysis and single-cell RNA sequencing demonstrated expansion of γδ T cells expressing the Vascular Cell Adhesion Molecule-1 (VCAM-1) and interferon-γ (IFNγ) genes. The expansion of *VCAM1+IFNG+* T cells led to B-cell activation and the production of multiple autoantibodies. We then showed that Regnase-1 directly targets VCAM-1 and IFNγ mRNAs thus explaining their dysregulated expression in the patient. While Regnase-1 cuts the VCAM-1 mRNA at its 3'UTR, we found that the 3'UTR of the IFNγ mRNA was not a Regnase-1 target. Instead, Regnase-1 recognised and cut a stem-loop structure in the coding sequence (CDS) of the IFNγ mRNA that we mapped to nucleotides positions 11 - 24.

These findings highlight a new autoimmunity mechanism in humans, where Regnase-1 deficiency causes expansion of the *VCAM1+IFNG+* T cells and their interaction with integrin α4β1-expressing B cells, which showed upregulation of IFN-response genes and activation, leading to systemic autoimmunity.

Conclusion

Our findings indicate that Regnase-1 can recognise mRNA stem-loop structures in CDS as well as 3'UTRs. This unexpected discovery will help to find additional mRNAs targeted by Regnase-1.

Our results show that Regnase-1 acts as a safeguard in the human immune system that prevents systemic autoimmunity. Our analysis also shows that *VCAM1+* T cells are expanded in some patients with systemic lupus erythematosus (SLE). These findings indicate that pathogenic mechanisms similar to those identified in our rare Regnase-1-deficient patient can cause common autoimmune diseases. Targeting this pathogenic mechanism may lead to novel precision therapies for such patients.

Molecular Basis of Autoimmune Disease Protection by MDA5 Variants

Joe Joiner, Rahul Singh, Alba Herrero del Valle, Ida Jobe, Chris Wallace, Yorgo Modis

Background

MDA5 belongs to the RIG-I-like receptor (RLR) family of pattern recognition receptors that detect the presence of cytosolic double-stranded RNA (dsRNA), a key signature of viral infection. MDA5 senses long dsRNA molecules longer than 100 bp on length and cooperatively assembles into ATP-sensitive filaments on dsRNA, to trigger downstream IFN-β and NF-κB inflammatory responses. The activity of MDA5 is finely calibrated to provide a fine balance between sensitivity and specificity of dsRNA recognition, and the *IFIH1* gene, encoding MDA5, is a hotspot for natural variants with clinical associations. Gain-of-function variants of MDA5 increase the sensitivity of MDA5 to endogenous dsRNAs and result in severe autoinflammatory disorders. Conversely, loss-of-function MDA5 variants result in a reduced risk of developing, certain autoimmune diseases (including type 1 diabetes), although we show that this is correlated with an increased risk of developing inflammatory bowel disease.

Summary

Using a combination of structural and biochemical methods, we show that autoimmune-protective variants of MDA5 reduce the IFN-β response to picornavirus infections but do so via distinct biochemical mechanisms that impact the stability of MDA5-RNA signalling complexes. While the E627* variant does not bind RNA, the I923V mutation results in increased ATPase activity, causing premature dissociation from RNA and, hence, decreasing the lifetime of signalling complexes and downstream interferon stimulated response. We additionally present cryo-EM structures of MDA5 I923V bound to dsRNA at different stages of ATP hydrolysis, which revealed smaller RNA binding interfaces, corroborating our biochemical data. Other investigated mutants did not affect cytokine induction, suggesting an alternative, indirect disease mechanism.

Conclusion

As a key sensor of cytosolic dsRNA resulting from infection or environmental stress, MDA5 is an attractive target for immunomodulatory therapies. Knowledge of the phenotypic traits associated with different MDA5 variants also has implications for treatment of autoimmune diseases. For example, RNA-based therapies could be dose-adjusted accordingly for patients with known MDA5 variants. Our results provide mechanistic insights into the molecular recognition of disease-associated MDA5 variants, to aid in the development of new, targeted therapeutic strategies to treat infectious, inflammatory, and autoimmune disease.

Neutrophils undergo a phenotypic switch following extended pathogen exposure

Maire Röder, Andrew Conway Morris, Muhammad Iqbal

Background

Neutrophils constitute the majority of circulating leukocytes and act as a critical first line of defence against infection. Their abundance, physical flexibility, and potent bactericidal capacity make them well adapted to this role. Crucially, there exists a fine balance between effective neutralisation of pathogens and mitigation of host tissue damage; disruption of this balance in either direction can have catastrophic consequences. However, both mechanisms to enhance the killing power of neutrophils and mechanisms to prevent tissue damage can become maladaptive. In the context of sepsis, which is defined as organ failure secondary to severe infection, neutrophil dysfunction and host tissue damage paradoxically coexist, resulting in simultaneous overwhelming infection and systemic inflammation and driving mortality.

Our group aims to understand the functional responses of neutrophils to the common pathogen *Staphylococcus aureus* and delineate the signalling pathways that underpin these. We also hope to examine heterogeneity within neutrophil populations and understand how they communicate with each other and other cells. By understanding these fundamental aspects of neutrophil biology we hope to be able to inform novel therapies to rescue neutrophil function and prevent maladaptive responses in the context of severe infection.

Summary

Following 2 hours of exposure to heat-killed *S aureus*, neutrophils significantly reduce their phagocytosis of subsequent homologous (*S. aureus*) and heterologous (*E. coli*) challenges. This is accompanied by a reduction in phagosomal acidification.

We examined the phosphoproteomic responses following short (15 mins) and prolonged (2 hrs) exposure to *S. aureus*, and identified marked reductions in protein phosphorylation and overall kinase activity at the later timepoint. Phosphoproteins increased at 2 hrs mapped to counter-regulatory and inhibitory pathways, and the negative regulatory kinase Lyn was phosphorylated.

Notably, proteomic and transcriptomic profiles at the late time point did not recapitulate the 'deactivation' phenotype identified in the phosphoprotein and functional assays. Proteins exhibiting decreased abundance at 2 hrs included cytokines, notably the chemokine CXCL8, and cytokine signalling molecules. Transcriptional signatures reflected these changes, with enrichment for NFKappaB and AP1 (FOS JUN) dependent genes.

These data point to neutrophils undergoing a phenotypic switch following prolonged *S. aureus* exposure, underpinned by distinct signalling pathways. The switch is characterised by reduced phagocytosis and phagosomal maturation and increased cytokine signalling.

Conclusion

Our findings in healthy donor neutrophils mirror the reported deactivation of kinase activity in neutrophils from patients with sepsis, and provide insights into the signalling that underpins these changes. The simultaneous switch to a pro-inflammatory phenotype is a novel finding, and should be validated *in vivo*. However, this suggests that the changes observed in sepsis may constitute an initially adaptive response aimed at preventing ongoing pathogen ingestion beyond neutrophils' bactericidal capacity, whilst simultaneously signalling for the recruitment of fresh neutrophils. This may become maladaptive in the context of overwhelming infection, leading to widespread neutrophil paralysis whilst simultaneously driving systemic inflammation.

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Short talk abstracts: Session 3

Oral vaccination with engineered bacteria induces CNS-protective T cells against meningitis

Qianchang (Dennis) Wang, Nathan Richoz, Xiaoyu Chen, Peter Nguygen, Miles Bremridge, Tetsuo Hasegawa, Felix Scharte, Rongzhen Tian, Karen Neish, Jason Chin, Felix Randow, James Collins, Menna Clatworthy

Background

Bacterial meningitis is a devastating condition that kills hundreds of thousands of individuals worldwide, particularly children in developing countries. There are currently no clinically-approved vaccines for *listeria monocytogenes*, a significant cause of neonatal meningitis with a particularly high mortality. The dural meninges contain multiple populations of immune cells, including gut-derived IgA-secreting plasma cells and CD4 T cells, that inhibit the entry of bloodborne pathogens into the central nervous system (CNS). Here we sought to investigate whether oral delivery of an engineered bacteria, could be used to generate effector T cells targeting meningitis-causing organisms.

Summary

Using novel modifications of attenuated, clinically-validated salmonella vaccine strains to enable bacterial surface display or intra-cytoplasmic delivery of listeriolysin-O (LLO) peptides, we demonstrate that oral vaccination in mice effectively elicits antigen-specific T cells in the gut, spleen and the meninges. This included LLO-specific CD8 T cells that localize to the dural vasculature, protecting the CNS from subsequent intravenous challenge with *L. monocytogenes*.

Conclusion

These findings introduce a practical, scalable approach to meningitis vaccination, especially in low-resource settings. By harnessing the gut-CNS axis, the study demonstrates for the first time that CNS CD8 T cells can be primed via the gut. At the intersection of tissue immunology and synthetic biology, this project provides a platform that could be adapted to other neuropathologies.

Characterising tight junctions in the human airway epithelium in health and disease

Leah Hurst, Lajos Kalmar, Wenrui Guo, Holly Giles, Alice Chernaik, Emma Gould, Vito Mennella, Frank McCaughan

Background

The respiratory airway epithelium lining the conducting airways plays a crucial role in human health. It acts as a biophysical barrier, separating the internal and external environments of the respiratory tract, and serves as the first line of defence against inhaled pathogens and environmental pollutants. The physical integrity of this barrier depends upon the intercellular junctions, specifically the tight and adherens junctions, which regulate paracellular permeability across the epithelium and cell-cell adhesion respectively.

Disruption and dysfunction of airway epithelial cell-cell junctions is implicated in the pathogenesis of airway diseases, including asthma and chronic obstructive pulmonary disease (COPD). Furthermore, data from AstraZeneca indicates that tight junction disruption can be used as a predictive readout of toxicity for pre-clinical compounds within their inhalation pipeline.

Despite the importance of airway epithelial cell-cell junctions in respiratory disease and inhalation toxicity prediction, their composition, nanoscale organisation and molecular mechanism of disruption has not been characterised within physiologically relevant *in vitro* models of the human airway epithelium.

Summary

The main component of tight junctions are claudins. This protein family consists of 26 members that are expressed in a tissue-specific manner. To identify which claudins were expressed in the human airway epithelium, we analysed single cell RNA-sequencing (scRNA-seq) data from the integrated Human Lung Cell Atlas (HLCA) which revealed that claudins 1, 3, 4, 7 and 10 were the main claudins expressed in the human airway epithelium. Pseudobulk and differential expression analysis revealed that there were cell type specific differences in expression, with claudin 3 more highly expressed in multiciliated cells and claudin 10 exclusively expressed in secretory cells.

We have established protocols to expand, culture and differentiate primary airway cells from human donors into pseudostratified airway epithelium maintained at the air-liquid interface (ALI). scRNA-seq analysis shows that these cultures faithfully reproduce the cell types in the adult airway. Importantly, the expression pattern of claudins in ALI cultures was consistent with the HLCA data, indicating the utility of ALI models to investigate tight junctions.

To determine the localisation of claudins we used immunofluorescence to reveal that claudins 1, 3, 4 and 10 all localise to the tight junctions, whereas claudin 7 localises to lateral membranes. Consistent with the scRNA-seq data, claudin 10 was only found in the tight junctions of secretory cells and claudin 3 protein levels were higher in the tight junctions of multiciliated cells compared to secretory cells.

As tight junctions lie below the diffraction limit of conventional light microscopy, their *in situ* organisation can be studied by super-resolution approaches. We are constructing a nanoscale map using SIM microscopy of tight junction protein localisation in healthy *in vitro* models of the human airway epithelium.

Using genetically manipulated airway cells or primary cells from well-phenotyped patients, we have begun investigating how tight junctions are disrupted within respiratory diseases.

Conclusion

The structure of tight junctions in the airway and mechanism of increased airway permeability is poorly understood. This has implications for disease pathogenesis and the toxicology of inhaled therapeutics.

In airway disease, the cell type composition of the epithelium changes markedly. The cell type differences in claudin composition may therefore contribute to the increased permeability observed in diseases like COPD.

A nanoscale map of tight junction proteins will provide the first high-resolution insight into their organisation in the airway. We plan to compare this map with disease models and further investigate protein-protein interactions at the junction using proximity labelling techniques.

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Head Injury and its Impact on Neurodegeneration, Cognition, and Brain Structure: Evidence from the UK Biobank

Daniel Whitehouse, D Stubbs, RR Garcia, CA Morillo, V Warrier, DK Menon, R Bethlehem, VFJ Newcombe

Background

There is increasing evidence demonstrating that head injury should no longer be considered as a single acute event, but a disease process that extends through a patient's lifetime. This includes an increased long-term risk of neurodegenerative diseases, including dementia, Motor Neurone Disease (MND), and Parkinson's disease. Regarding neurodegenerative disease risk, there are currently over 15 years of follow-up data available in the UK Biobank. This enables the identification of incident cases of neurodegenerative disease across a large UK population over a sustained period. Additionally, basic neurocognitive testing and neuroimaging, including diffusion tensor imaging (DTI), was performed in a subset of participants, allowing for an evaluation of the long-term impact of head injury on cognitive performance and neuroimaging findings. By utilising the linked healthcare records present in the UK Biobank study, this study aims to: (1) assess the risk of neurodegenerative disease following head injury, (2) examine the long-term impact of head injury on cognitive performance, and (3) examine the long-term impact of head injury on neuroimaging findings in the UK Biobank cohort.

Summary

Non-fatal head injury and incident neurodegenerative disease were identified using hospital inpatient records, primary care records, and self-reported questionnaires. The results of 5 neurocognitive tests were assessed, including: Reaction Time, Pairs Matching, Numeric Memory, Prospective Memory and Fluid Intelligence. Diffusion Tensor Imaging was performed in a subset of patients, with assessment of Mean Diffusivity (MD) across 68 cortical regions of interest and Fractional Anisotropy (FA) and MD in 27 white matter tracts. The association between head injury and incident neurodegenerative disease was assessed using Cox proportional hazards models, with head injury defined as a time-varying exposure and adjustment for relevant covariates. Multivariable linear regression was used to assess the association between a history of head injury and neurocognitive test performance. Finally, associations between prior head injury and MRI-derived microstructural metrics were evaluated using linear regression models.

During follow-up, 5.2% with head injury vs. 2.8% without had a diagnosis of neurodegenerative disease, with a 1.78 times higher risk (95% CI: 1.60-1.97) of neurodegenerative disease in those with a history of head injury. Females had a stronger association: HR 2.08 (95% CI: 1.76–2.47) vs. males HR 1.62 (95% CI: 1.41–1.86), interaction p = 0.024. Risk increased with multiple head injuries: HR 2.62 (95% CI: 1.91, 3.59) for ≥2 injuries vs. HR 1.71 (95% CI: 1.53-1.91) for one injury, trend p < 0.001. Head injury was associated with an increased reaction time (p < 0.001), lower prospective memory recall (adjusted OR 0.82, 95% CI 0.73-0.91, p < 0.001), lower fluid intelligence (p = 0.002), and poorer overall cognitive performance (p = 0.001, UKB-5 test). Head injury was significantly associated with higher cortical MD and altered MD/FA in white matter tracts.

Conclusion

In conclusion, participants in the UK Biobank cohort with a confirmed history of non-fatal head injury had an increased risk of incident neurodegenerative disease, worse performance across multiple cognitive tests, and evidence of microstructural damage of both white matter tracts and cortical grey matter as compared to those with no documented head injury history. Despite limitations in case acquisition, these findings align with broader evidence linking head injury to neurodegenerative disease and highlight the potential value of long-term cognitive assessment after head injury.

Acute Thalamic MRI Markers of Chronic Post-Concussive Symptoms

RE Woodrow, S Winzeck, AI Luppi, LRB Spindler, JTL Wilson, VFJ Newcombe, CENTER-TBI MRI Sub-study Participants and Investigators, JP Coles, DK Menon, EA Stamatakis (PACE)

Background

Mild traumatic brain injury (mTBI), often leads to persistent symptoms such as depression, cognitive impairment, headaches, and fatigue, with over half of patients reporting multiple symptoms six months post-injury. Prognostication remains poor, with clinicians frequently overestimating recovery, and current predictive models and treatments lacking precision and biological grounding. The thalamus, a central hub for cortical communication and cognition, is particularly vulnerable in mTBI but remains under-investigated.

Functional MRI imaging, especially resting-state fMRI, reveals widespread thalamic hyperconnectivity in the acute and subacute phases, correlating with symptom severity and recovery trajectories. However, previous studies are limited by small sample sizes, lack of longitudinal data, and confounding factors such as pre-existing psychiatric conditions. Furthermore, the neurochemical basis of thalamic connectivity changes and their therapeutic relevance remain unexplored.

This study leverages data from the CENTER-TBI project to investigate nuclei-specific thalamic connectivity, its relationship to symptom profiles, and potential neurochemical correlates. The findings aim to improve prognostic accuracy and identify biologically informed therapeutic targets, addressing a critical gap in the care and treatment of mTBI patients.

Summary

In a cohort of 108 mTBI patients with normal CT scans and Glasgow Coma Scores of 13–15, we found that despite no structural imaging differences between mTBI patients and controls (n=76), functional MRI revealed widespread thalamocortical hyperconnectivity in the acute phase, particularly involving the bilateral ventral anterior and right ventral lateral dorsal thalamic nuclei. These changes were not associated with demographic or injury-related variables and were most pronounced in patients with cognitive and emotional symptoms.

At six months post-injury, 47.2% of patients showed incomplete recovery, with fatigue, poor concentration, and headaches being the most prevalent symptoms. Blood biomarkers (NSE, S100B, GFAP, Tau, UCH-L1, NFL) did not differ between outcome groups, highlighting the need for novel functional and neurochemical markers. Patients with persistent symptoms exhibited greater thalamic connectivity to cortical regions involved in cognition and emotion, while somatic symptoms showed more modest associations.

Neurotransmitter mapping revealed that hyperconnected regions were enriched in noradrenergic and dopaminergic targets, with strong positive correlations to noradrenaline transporter density across symptom subgroups. Emotional symptoms were also negatively associated with serotonergic receptor density. These findings suggest that thalamic hyperconnectivity may reflect underlying neurochemical vulnerabilities.

A subset of patients (n=31) underwent serial imaging at 6 and 12 months. Only those with persistent symptoms showed significant reductions in thalamic connectivity over time, while structural imaging remained unchanged. These results underscore the sensitivity of functional imaging in capturing symptom-related brain changes and support the prognostic value of thalamocortical connectivity and its neurochemical context in mTBI.

Conclusion

Quantitative acute thalamic connectivity may offer a valuable tool for understanding and predicting chronic post-concussive symptoms in mTBI. Longitudinal studies, like this one, reveal that symptom-relevant neurological changes extend beyond six months. Future research should validate these findings in independent cohorts and integrate multimodal imaging to explore links between functional connectivity and microstructural injury. Neurochemical mapping, including noradrenergic and GABA-related pathways, and assessments of neurotransmitter metabolites, may further clarify mechanisms. Investigating brainstem-thalamus connectivity could enhance predictive models and guide targeted therapies, positioning thalamic alterations as a key component in advancing mTBI care.

Annual Research Day 2025

The survival discrepancy between Pulmonary Arterial Hypertension patients eligible for clinical trials and clinical reality

Eckart De Bie, Rowena Jones (HLRI), Prof Alex Rothman (Sheffield), Dr Mark Toshner (HLRI), Dr Chris Wallace (CITIID)

Background

In drug development and authorisation, there is historically a gap between the clinical trial population that evidence is generated in, and the population that therapies are applied to. It is important to understand this gap, as this has implications for external validity of clinical trials.

Our aim was to clarify this for patients with pulmonary arterial hypertension (PAH), a rare but severe disease associated with significant morbidity and mortality. Significant advances in the field of PAH, including licensing by the MHRA of a novel activin ligand trap have been made. However, the costs of these therapies are high (estimated to cost $250,000 a year) and trial inclusion/exclusion criteria have been restrictive.

Therefore, using the UK National Cohort Study of Idiopathic and Heritable PAH, we investigated long-term outcomes in patients who were eligible or ineligible for four recent major regulatory approved therapies in five registration studies (SERAPHIN, AMBITION, TRITON, PULSAR, and STELLAR). Differences in short term clinical worsening events and uptitration of medical therapy were also investigated.

Summary

Out of all PAH patients enrolled in the UK IPAH/HPAH cohort (n=1,015), 55% - 85% of PAH patients would not have been eligible to participate in the registration trials.

The most common reason for trial ineligibility were out of range haemoglobin levels and clinical functional parameters in particular the 6 minute walk test (6MWT).

Trial eligibility did not associate with the regulatory approved primary endpoints (treatment response as determined by 6MWT and clinical worsening events) or disease risk score improvement, but was associated with significantly improved long-term survival (HR 0.66-0.91 in Cox-Proportional Hazard models) after adjustment for age and sex.

These analyses were validated in an independent UK cohort including all types of PAH, including connective tissue disease PAH (ASPIRE, n=1,320), showing comparable results.

Conclusion

Survival is in PAH is worse in real world populations who do not fulfil trial eligibility criteria compared to those eligible for trials. However, regulatory-approved endpoints for treatment response are comparable between populations who would and would not be eligible for the major registration trials. This has important implications for the external validity of PAH trials.

We plan to conduct a trial emulation study for patients treated with PAH drugs for which they were ineligible for trial inclusion.

StratosPHere 1 Study: A novel BMP target engagement biomarker panel for use in clinical trials in PAH

Rowena J. Jones, Eckart M.D.D. De Bie, Nina Deliu, Anthony Y.K.C. Ng, Benjamin J. Dunmore, Stefan Gräf, Christophe Guignabert, Marc Humbert, Laurent Savale, Ly Tu, Athénäis Boucly, Joseph Newman, Gary Polwarth, Paul D. Upton, Allan Lawrie, Christopher J. Rhodes, Martin R. Wilkins, Sarah K. Binmahfooz, Alexander M.K. Rothman, Anna Hemnes, Sofía S. Villar, James West, UK National Cohort Study of Idiopathic and Heritable PAH Consortium, The Uniphy Clinical Trials Network and Mark R. Toshner

Background

Pulmonary arterial hypertension (PAH) is a rare, life-limiting disease where imbalances in the Transforming Growth Factor-b (TGFb) superfamily pathways have causal roles in hereditary and idiopathic forms. These pathways are emerging attractive candidates for therapeutic intervention but there is an unmet need for clinically relevant and practical biomarkers that can measure target engagement. A major challenge has been the inaccessibility of lung tissue in disease for molecular profiling. Here we explore the surrogate capacity of peripheral blood Bone Morphogenetic Protein (BMP) pathway-specific markers.

Summary

Plasma proteomic analysis demonstrates widespread pleiotropic alterations of TGFb/BMP modulators. Downstream Bone Morphogenetic Protein Receptor type-II (BMPR-II) canonical and non-canonical signalling is altered and measurable in whole blood, and transcriptomic signatures cluster by discrete BMPR-II gene modules. We present discovery and international replication cohorts for the transcriptomic BMPR-II signalling signatures and derive a composite transcriptomic biomarker panel that is repeatable, reproducible, longitudinally stable and expressed in correlated gene modules in PAH which associate with clinical outcomes, most notably mortality.

Conclusion

The assay performance characteristics of the biomarker panel make it feasible for early phase, target engagement clinical trials and we have utilised it in a pilot study of sotatercept-treated patients that suggests the therapy does not mechanistically rebalance/increase BMPR-II pathway signaling, but rather shows a reduction, likely due to depletion of circulating BMP9 and BMP10.

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Short talk abstracts: Session 4

Low-dose Interleukin-2 expands and modulates human atherosclerotic plaque regulatory T cells: results from the ELLIPSE trial

Ayden Case, James W. O'Brien, Fiona T. W. Charlier, Ali B.A.K. Al-Hadithi, Mohammed M. Chowdhury, Stephen Newland, Zixuan Huang, Gemma Basatemur, Ayoola I. Awopetu, Jonathan R. Boyle, Nicholas R. Evans, Ziad Mallat, Tian X. Zhao

Background

Atherosclerosis, the leading cause of myocardial infarction and stroke, is now recognized as a chronic inflammatory disease. Regulatory T cells (Tregs) are powerful modulators of the immune response and restrain inflammation. In mouse models, increasing the number of Tregs reduces atherosclerotic plaque burden. Low-dose interleukin-2 (ld-IL-2) has been shown to selectively increase circulating Tregs in patients with several autoimmune diseases. In the LILACS study, we showed that ld-IL-2 treatment after acute coronary syndrome augmented circulating, suppressive Tregs bearing T cell receptor (TCR) motifs linked to atherosclerosis-related antigens. The IVORY study showed that ld-IL-2 was able to reduce vascular inflammation following acute myocardial infarction as measured using 18F-FDG-PET.

However, it is unknown whether ld-IL-2 can directly modulate Tregs in the diseased tissue either in atherosclerosis or other autoimmune diseases. Indeed, it has never been shown if any drug can directly modulate immune cells in human atherosclerosis. Therefore, using the latest breakthroughs in single-cell RNA sequencing (scRNA-seq) technologies, we conducted *The Effect of Low-dose Interleukin-2 on the Immune Landscape of Human Atherosclerotic Plaques at Single Cell Resolution* (ELLIPSE) study, a randomised, controlled, interventional clinical trial.

Summary

In the ELLIPSE trial, patients with either stroke or transient ischemic attack planning to have a clinically indicated carotid endarterectomy were recruited and randomised 1:1 to either standard of care (control) or treatment with 5 consecutive days of aldesleukin (ld-IL-2) at 1.5MIU/day subcutaneously before their planned surgery. Patients' plaques (and paired blood) were taken at the time of surgery, digested into a single-cell suspension, and processed using the Parse Biosciences WT+TCR scRNA-seq platform. The primary outcome was the effect of systemic ld-IL-2 on plaque Tregs.

In total, 27 patients were initially recruited, with 19 undergoing randomisation. Of the 10 patients randomised to control, all patients' plaques were taken at time of surgery. Two plaques had to be later withdrawn due to poor quality. Nine patients were randomised to ld-IL-2. Two plaques were withdrawn due to poor quality or protocol variations in dosing schedule.

This resulted in a final cohort of 15 plaques, 7 from the treatment group and 8 from the control group. The cohort was closely matched for age, sex, and symptom status between groups. No serious adverse events were reported. The most common adverse event was a temporary injection site rash. This the first report of the use of aldesleukin in stroke and, with the limited data we have collected, the safety profile appears favourable.

Ld-IL-2 treatment selectively increased Treg numbers in atherosclerotic plaques ($p<0.05$) and in the circulation ($p<0.001$). The ld-IL-2-treated plaque Tregs upregulated pathways previously associated with a response to ld-IL-2, including HALLMARK "IL-2/STAT5 Signalling". An upregulation of genes associated with effector functions including *CD25* and *CTLA4* was observed in ld-IL-2-treated Tregs. This was accompanied by a downregulation of genes which supress the effector program, including *BACH2*.

Conclusion

This is the first data showing the ld-IL-2 can induce tissue-based Tregs in any disease setting. It is also the first study to show that systemic immune modulation in patients with atherosclerosis can alter plaque immune cells at a single-cell level. Preclinical data shows that Tregs are beneficial after stroke, and this trial is the first use of this strategy.

Next, we will begin analysing the single-cell TCR data to infer clonal expansion and the relationship between circulating and plaque-resident cells. We will also examine communication between induced Tregs and key effector cells like macrophages. Finally, we plan to leverage spatial transcriptomic techniques to further elucidate ld-IL-2's effects on plaque tissue.

3D imaging of the synovium defines an intricate immunological defence system at the blood-joint barrier

Tetsuo Hasegawa, Menna Clatworthy

Background

Joint pain or inflammation is a common and early feature of a variety of systemic diseases. These include autoimmune diseases, such as systemic lupus erythematosus (SLE), as well as infection in organs distant to the musculoskeletal system, including enteric or genitourinary infections, which manifest as reactive arthritis. However, why joints are highly responsive to systemic inflammation and where in the joint the inflammation starts are still unknown.

Summary

We sought to address these questions by developing a whole mount imaging system of the membrane that covers the joint cavity, called synovium, to profile the vascular, neuronal and immune microarchitecture. This revealed that highly permeable capillaries were specifically located at the lining-sublining interface, in the periphery of the synovium, enabling entry of circulating stimuli into the joint. This area of vulnerability was occupied by three subsets of macrophages that demonstrated distinct responses to systemic immune complex challenge and reciprocally interacted with nociceptor neurons, forming a blood-joint barrier (BJB) to defend joint tissue.

Conclusion

Further work is needed to explore how this sentinel unit becomes disrupted in joint diseases like rheumatoid arthritis, and whether and how dysregulation of neuro-macrophage interactions play a role in the joint pain associated with these conditions.

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A crucial role for thyroid hormone signalling in Natural Killer Cell Biology

Stacey McIntyre*, Emily Thomas*, Esme Nichols, Kassandra Verzygianni, Anthony Ng, Simon Clare, Paul Lyons, Krishna Chatterjee, Anneliese Speak, Alice Denton^, David Thomas^

*equal contribution
^equal contribution

Background

The endocrine system can affect immune function but the role of thyroid hormone in immunity is not well defined. The starting point for our work was the unusual immunological phenotype of Duoxa2-/- mice. The Duox2-Duoxa2 system generates reactive oxygen species at several epithelial surfaces, likely for host defence, but it is also needed for the iodination of thyroid hormone. Using several orthologous experimental models, we show that thyroid hormone plays a non-redundant and hitherto undescribed role in lymphocyte function.

Summary

Duoxa2 is essential for making reactive oxygen species at epithelial surfaces and in the thyroid gland and is essential for normal thyroid function. *Duoxa2* deficient mice are hyper-susceptible to melanoma metastasis, the most susceptible of any mouse in the Sanger Institute's melanoma metastasis pipeline. This occurs because both natural killer (NK) cells and CD8+ T cells show impaired function and maturation in *Duoxa2*-/- mice, especially in the expression of the killing machinery comprising perforin and granzyme B. *Duoxa2* deficient mice are hypothyroid and their abnormalities in NK cell biology can be recapitulated by rendering mice hypothyroid by chemical means. These abnormalities can be corrected by replacing thyroid hormone. We investigated the transcriptional pathways controlled by thyroid hormone in NK cell progenitor cells and more mature NK cells using both bulk and single cell RNA-seq.

Transcriptionally, thyroid hormone dictated several aspects of NK cell development. In NK progenitor cells, it influenced the insulin like growth factor signalling pathway and SCF-kit signalling as well as both the interleukin 2 and interferon gamma pathways. In more mature NK1.1+ bone marrow NK cells, we saw marked differences between control and *Duoxa2*-/- cells including disruption of many pathways relating to the cell cycle. Human leucocytes, including NK cells, express thyroid hormone receptors. Patients with mutations in thyroid hormone receptor signalling experience frequent ENT infections and we are dissecting why this is the case in collaboration with Professor Krish Chatterjee

Conclusion

We have shown a novel role for thyroid hormone signalling in immune cell biology. This is conserved between mouse and human cells and begins to explain the immune phenotypes of patients with rare thyroid disorders. Dissecting the pathways controlled by thyroid hormone not only open up an exciting new avenue of research in immune physiology but are also important for maximising the efficacy of NK cell based cellular therapies.

The role of hypoxia and HIF in sympathoadrenal development

Emma Hodson, Rahul Manamperige, James Nathan

Background

Normal development occurs in physiological hypoxia, but severe hypoxia has pathological consequences. Gestational hypoxia results in sympathetic hyperinnervation and cardiovascular dysfunction in fetal and postnatal life, but the underlying mechanisms remain largely elusive.

Hypoxia-inducible factors (HIF-1/HIF-2) are oxygen-regulated transcription factors that coordinate the transcriptional response to hypoxia. HIFs mediate adaptive cardiorespiratory physiology in the adult but are also widely active in the hypoxic environment of embryogenesis. These physiological oxygen gradients, activating HIF, could contribute to the environmental cues that determine cell fate, but this has not been studied systematically.

The vertebrate-specific HIF-2 is highly expressed in developing sympathoadrenal tissues and is essential for fetal catecholamine homeostasis. HIF-2 activating mutations cause heritable catecholamine-producing tumours (Pheochromocytoma/ Paraganglioma), with anatomical and biochemical features of immature cell types. Similarly, mouse models of these mutations reveal sympathoadrenal abnormalities including expansion of disorganised adrenal neuroendocrine cells with atypical gene expression, including loss of PNMT (catalysing adrenaline biosynthesis). These features suggest abnormal sympathoadrenal precursor migration and differentiation, but it is unclear which developmental stage is affected, whether this causes developmental arrest or trans-differentiation, and the consequences for sympathetic function.

We hypothesize that hypoxia regulates sympathoadrenal development via activation of HIF-2, with consequences for post-natal physiology and disease.

Summary

We use a protocol to differentiate human embryonic stem cells into sympathoadrenal cells with markers of neuronal (PRPH+) and neuroendocrine identity (chromogranin A+) via defined intermediate stages, including trunk neural crest (NC). We then submit each stage to hypoxic and pharmacological interventions to activate HIF.

We find that moderate hypoxia (1-5%) promotes lineage commitment during all stages of sympathoadrenal differentiation, possibly reflecting physiological oxygen exposure in normal development.

In normoxia, the HIF-a subunit is targeted for degradation by the oxygen-sensitive PHD enzymes. Roxadustat is a small molecule PHD inhibitor that stabilises HIF independent of oxygen, allowing us to assess HIF-specific effects.

Cells at each stage of sympathoadrenal development *in vitro* show differential sensitivity to pharmacological HIF activation by Roxadustat.

Trunk NC cells are highly sensitive, with evidence of Roxadustat-induced toxicity at low-moderate doses. We observe dose-dependent reduction in expression of NC markers (*SOX10, TFAP2A*), impaired cell growth in cells treated with Roxadustat for 20h, and cell death with longer exposure. We are now investigating metabolic phenotypes associated with this response, as prior work in avian models shows differential metabolic requirements between regions and stages of neural crest development, which could be susceptible to HIF-dependent re-programming.

In contrast, Roxadustat favours growth of sympathoadrenal progenitors and induces up-regulation of genes for sympathoadrenal specification (*PHOX2B, TH*) and both neuronal (*PRPH*) and neuroendocrine (*CHGA*) differentiation.

We are now developing a genetic model to interrogate HIF isoform specificity using inducible expression of constitutively stabilised HIF-2a (HIF-2dPA). We are also deploying this system in parallel experiments on chicken embryos to study HIF-dependent effects on NC migration and multi-lineage differentiation *in vivo*. We have established a method for genetic targeting of the NC enabling stage-specific inducible expression of HIF-2dPA within the developing embryo, accompanied by a lineage tracer that we can identify in sympathoadrenal cells.

Conclusion

We have developed experimental systems to determine how oxygen sensing controls sympathoadrenal development, potentially programming pathologies including phaeochromocytoma/paraganglioma and hypertension.

We observe stage-specific effects of pharmacological HIF activation, which favours growth and differentiation of sympathoadrenal progenitors. We also find striking HIF-sensitivity of the neural crest, which gives rise to diverse cell types in the autonomic nervous system, heart and vasculature. A key question is whether HIF(2) biases cell fate across these systems to program post-natal physiology. Next, we will use the chicken model to explore effects of HIF(2) activation across multiple lineages and the consequences for cardiovascular physiology at term.

Annual Research Day 2025

Flash talk abstracts

Investigating inequality in access to specialist surgery: update on a registry for chronic subdural haematoma

Daniel Stubbs, JP Coles (PACE), BM Davies (Neurosciences), PJ Hutchinson (Neurosciences), Jugdeep Dhesi (BGS), I Moppett (RCOA and Nottingham)

Background

- Specialist surgery is only conducted in major centres – creating a hub and spoke model of referrals for expedited care
- An exemplar condition, chronic subdural haematoma, demonstrates significant outcome differences by referral route
- In our rural capture – high numbers of higher risk patients are referred from hospitals in rural/coastal areas where health needs are already higher
- It is unclear which other procedures might face similar challenges and whether outcome differences reflect baseline inequality or iatrogenic harm of referral

Summary

- Present an update on the impact and implementation challenges of a complex intervention bundle for chronic subdural haematoma in the East of England and the design of a national registry for the condition which will be launched in 2026
- Outline steps to use routinely collected hospital episode statistic data from England and Wales to identify other specialist surgeries with high transfer rates and understand how this varies across the country
- Describe the data infrastructure established to use causal inference to test the hypothesis that indirect referral for specialist surgery (via another institution) is associated with harm

Conclusion

- Nearly 2/3 of the population will have a surgical procedure in their lifetime and admission for surgery carries the risk for significant ongoing morbidity beyond the hospital stay
- It is crucial to understand whether it is possible to improve cross-centre surgical care and also where such strategies should be deployed to ensure that access to specialist surgery is equitable.

Pathophysiological Insights into Post-Traumatic Amnesia in Mild Traumatic Brain Injury: A CENTER-TBI Study.

Olivia Rowe (PACE), Virginia Newcombe, CENTER-TBI Investigators

Background

- Post-traumatic amnesia (PTA) is a state of disorientation, memory loss, and behavioural dysfunction that occurs after traumatic brain injury (TBI).
- PTA is a strong predictor of TBI severity and functional recovery, but its underlying pathophysiology is unclear.
- Clinical scales for assessing PTA have limitations, and PTA isn't associated with specific neuroimaging findings.
- Neuroimaging may be difficult given PTA's neurobehavioral symptoms, but blood biomarkers are a practical alternative.
- Studies have shown elevated blood biomarkers like neurofilament light (NfL), a marker of white matter injury, in patients with PTA.
- It's hypothesized that PTA's underlying dysconnectivity may relate to white matter damage.

Summary

- Blood biomarkers from CENTER-TBI were analyzed in relation to PTA status.
    - Blood biomarkers: maximum GFAP and UCH-L1 (<24 hrs post-injury) and NfL and tau (5–31 days)
    - PTA: defined on ED admission as ongoing/suspected, resolved, or none
- Linear models were fitted in R per biomarker. Estimated marginal means were computed with post hoc comparisons (Tukey adjusted).
- Multinomial logistic regression assessed biomarker vs. clinical imaging performance.
- Blood biomarkers distinguished ongoing PTA from resolved/no PTA; GFAP also distinguished resolved from no PTA.
- NfL (AIC: 404.17), GFAP (414.55), and UCH-L1 (414.64) outperformed clinical imaging (420.54) in identifying PTA status.

Conclusion

- While research has identified independent relationships between TBI severity and PTA and TBI severity and blood biomarkers, there is limited work exploring the relationship between PTA and blood biomarkers.
- These findings provide evidence of a pathophysiological gradient of PTA severity.
- PTA status is associated with distinct differences in markers of neuroaxonal and astroglial injury.
- The results highlight that biomarkers, particularly NfL, are better classifiers for distinguishing PTA status than clinical imaging, supporting the notion that PTA is likely related to white matter injury.
- Future work will investigate the interplay between blood biomarkers, structural atrophy, PTA, and functional outcomes from CENTER-TBI.

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CD47 inhibits clearance of senescent vascular smooth muscle cells and promotes neointima formation

Yee-Hung Chan, Anuradha Kaistha, Jordi Lambert Sebnem Oc, Kirsty Foote, Nichola Figg, Lauren Kitt, Helle F Jørgensen, Martin Bennett

Background

Senescent vascular smooth muscle cells (VSMCs) accumulate in atherosclerosis and aging vessels.

We previously found that mice with persistent telomere damage in VSMCs had enhanced senescence and inflammation in neointimal lesions resulting from carotid artery injury.

Interactions between senescent VSMCs and phagocytes are not well characterised.

We hypothesised that senescent VSMCs persist by evading recognition and clearance by phagocytes.

We sought to determine whether and how senescent VSMCs are eUerocytosed, and identify potential cell surface ligands that may inhibit their clearance.

Summary

We evaluated the expression of eUerocytosis inhibitory signals in senescent VSMCs.

CD47 specifically, was upregulated upon both induction of the DNA damage response and senescence.

By use of co-incubation assays, we found that senescent VSMCs resisted eUerocytosis, whilst CD47 depletion promoted their eUerocytosis by macrophages.

CD47 blockade in mice with persistent telomere damage in VSMCs following carotid artery injury attenuated neointima formation and proinflammatory processes in the leukocytes.

Conclusion

Inhibiting CD47 promotes eUerocytosis of senescent VSMCs.

CD47 blockade in senescence-prone mice following carotid artery injury reduces neointimal lesion formation resulting from carotid artery injury and elicits anti-inflammatory eUects on the leukocytes.

Our findings suggest CD47-mediated eUerocytosis evasion contributes to the persistence of senescent VSMCs.

Targeting CD47 may promote the clearance of senescent VSMCs and subsequently eliminate their pro-inflammatory/atherogenic eUects.

Further work is needed to delineate mechanisms underlying the upregulation of CD47 and other inhibitory signals which may be exploited by senescent VSMCs to escape immunorecognition and clearance.

The mitochondrial deglutarylase ABHD11 is a novel route to target T cell metabolism

Hudson Coates, Guine Grice, Eleanor Minogue, Randall Johnson

Background

- Targeting metabolic pathways to reduce inflammation is an effective therapeutic strategy.
- Methotrexate (a dihydrofolate reductase inhibitor) has treated immune diseases for over 40 years, yet its use is limited by a lack of target specificity and resultant toxicity.
- There is a need to identify alternative metabolites and metabolic pathways that are targetable for modulating immune function.
- 2-Oxoglutarate (a-ketoglutarate), a small-molecule metabolite at the interface of mitochondrial metabolism and epigenetic reprogramming, is a promising candidate.
- Previous work established that 2-oxoglutarate levels are regulated by the serine hydrolase ABHD11; however, the mechanism and its effect on immune cell fate was unknown.

Summary

- We uncovered ABHD11 as a novel candidate for targeting metabolism in immune disease.
- A newly discovered enzymatic activity of ABHD11 is deglutarylation that preserves the activity of a 2-oxoglutarate-metabolising enzyme in mitochondria.
- When ABHD11 is inhibited in CD8+ T cells using a selective and non-toxic inhibitor (ML226), 2-oxoglutarate is diverted towards fatty acid and triglyceride synthesis.
- This is accompanied by reduced effector capacity at physiological oxygen concentrations and a shift towards a central memory phenotype.
- The immune-dampening effects of ABHD11 inhibition are also observed in CD4+ T cells and autoimmune disease models developed by collaborators at the University of Swansea.

Conclusion

- Our work establishes the ABHD11 inhibitor ML226 as a modulator of mitochondrial 2-oxoglutarate metabolism and immune cell fate.
- Using ML226 to shift CD8+ T cells from an effector phenotype to a central memory phenotype will be advantageous for extending immune cell longevity (e.g., CAR-T cell therapy) or suppressing harmful immune responses.
- The specificity and minimal toxicity of ML226 adds to its appeal as a therapeutic strategy for targeting metabolism in immune disease.
- Future work will examine the molecular mechanism by which 2-oxoglutarate metabolism is rewired in ML226-treated T cells, and the effects of ML226 on other immune cell subtypes.

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NK cells evasion and exhaustion in the Tumour MicroEnvironment

Vincent Zecchini, Yundi Huang, Jia Jhing Sia and Annie Speak

Background

- Natural Killer (NK) cells have an innate ability to seek and destroy cancer cells.
- NK cells exhibit decreased fitness and cytotoxicity after repeated engagements with target cells, a process called NK cell exhaustion.
- The tumour microenvironment (TME) creates a hostile environment for NK cells resulting in reduced fitness and functionality.
- Selective pressure can also promote the expansion of cancer cells with key mutations enabling them to escape detection.
- The aim of this project is to identify the pathways that modulate NK cell cytotoxicity to produce cells better equipped to detect and eliminate cancer cells more effectively.

Summary

- Developing protocols for the in vitro expansion of primary NK cells and NK cell exhaustion modeling and gene editing:
- Isolation of primary human NK cells from human blood samples.
- Treatment of NK cells with activating receptors to mimic repeated engagements with target cells or with cytokines or metabolites to simulate the TME conditions.
- Identification of phenotypic markers to allow exhausted vs non-exhausted NK cells distinction in a CRISPR/Cas9 screen.
- Optimisation of CRISPR/Cas9-mediated gene editing in human primary NK cells using viral transduction.
- Generation of Cas9-expressing lung and ovarian cancer cells lines to assess their sensitivity to NK cell-mediated killing.

Conclusion

- Identification of differentially regulated genes/pathways in NK cells following our exhaustion protocols using whole-genome sequencing.
- Using RNASeq data, design of a library targeting specific genes to perform a phenotypic CRISPR/Cas9 screen in exhausted NK cells.
- Perform a whole genome CRISP/Cas9 screen in lung/ovarian cancer cell lines to identify the genes/pathways underlying sensitivity or resistance to NK cell killing.
- The combined results from these screens will be crucial in the identification of targets that could potentially be modulated to boost NK cell fitness and cytotoxicity.
- The ultimate project aim is the design of CAR-NK cells with improved cytotoxicity towards cancer cells.

Investigating Kidney-Intrinsic Immune Responses in Sepsis-Associated Acute Kidney Injury

Ping-Huang Tsai, Benjamin J. Stewart, Linus Butt, James McCaffrey, Elvis B. Kidzeru, Elena Prigmore, Agnes Oszlanczi, Di Zhou, Elizabeth Tuck

Background

- AKI is a frequent complication of sepsis, often linked to reduced kidney perfusion.
- We address whether renal cell-intrinsic responses to LPS (lipopolysaccharide), independent of blood flow, initiate immune activation, injury, and fibrosis.

Summary

- We perfused discarded human kidneys ex vivo at body temperature with or without LPS.
- Single-cell and spatial transcriptomics identified strong early responses in glomerular endothelial cells (GECs) and Type A intercalated cells.
- GECs upregulated chemokines and orchestrated immune cell recruitment.

Conclusion

- Kidney-resident cells, particularly GECs, can initiate immune signaling after LPS exposure.
- This suggests a local driver of inflammation in sepsis-induced AKI.
- Our ex vivo perfusion model enables mechanistic studies and testing of interventions in early kidney injury.

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Synergistic Activation of NLRC4 and NLRP3 Inflammasomes in Autoinflammation Driven by NLRC4 Gain-of-Function Mutations

Weidong Jing, Marisa Dilucca, John Wright, Joseph Boyle, Clare Bryant

Background

Gain-of-function (GoF) mutations in inflammasome sensors such as NLRC4 can lead to uncontrolled inflammasome activation and severe autoinflammatory diseases, including macrophage activation syndrome. However, the molecular mechanisms by which these mutations alter NLRC4 structure and function remain poorly defined. This study addresses how the NLRC4 T337S GoF mutation affects inflammasome activation and whether it contributes to dysregulated innate immune responses through cross-talk with other inflammasomes.

Summary

Using CRISPR/Cas9 gene editing, we introduced the NLRC4 T337S mutation into human THP-1 cells. These cells exhibited exaggerated inflammasome activation, including enhanced ASC speck formation, caspase-1 activation, cytokine release, and pyroptosis, in response to NLRC4-specific stimuli.

Mechanistic studies revealed that T337S destabilised NLRC4-ADP binding, weakening its autoinhibitory state. Moreover, the hyperactivation was partially regulated by PKCδ-dependent phosphorylation. Interestingly, the mutation also triggered a hyperactive NLRP3 inflammasome, without causing global inflammatory pathway upregulation.

Conclusion

Our findings uncover a synergistic mechanism of NLRC4 and NLRP3 inflammasome activation driven by NLRC4 GoF mutations. This work highlights ADP-binding and phosphorylation as a key regulatory mechanism and positions dual inflammasome targeting as a potential therapeutic approach. Future studies will explore the in vivo relevance of this synergy and its implications for treating NLRC4-associated autoinflammatory syndromes.

Targeting Early Squamous Carcinogenesis: A Primary Human Cell Model for Lung Cancer Chemoprevention

Wenrui Guo, Holly Giles, Alice Chernaik, Namshik Han and Frank McCaughan

Background

Lung squamous cell carcinoma (LUSC) lacks effective targeted therapies or chemoprevention strategies, and remains a leading cause of cancer mortality. While genomic studies have identified key mutations in advanced and high-grade preinvasive LUSC, the earliest cellular and molecular events driving its initiation are poorly understood. A major barrier to progress is the absence of robust, human-relevant models to study early squamous carcinogenesis. This work addresses the critical need for a primary human cell-based model that mimics early LUSC initiation, enabling the identification of early disease markers and evaluation of potential chemopreventive interventions.

Summary

This study presents a novel primary human cell model for early squamous lung cancer (LUSC) development, using short-term carcinogen exposure on airway epithelial cells from normal and COPD donors. The model recapitulates early carcinogenic changes, including basal cell hyperplasia and the emergence of transcriptionally distinct abnormal basal cells. Single-cell RNA-seq and histological analyses confirmed these early cancer hallmarks. Crucially, treatment with an AGC kinase inhibitor reversed the abnormal phenotype without harming normal cells. This model provides a valuable tool for understanding early LUSC events and testing chemoprevention strategies, addressing a major gap in targeted interventions for this cancer type.

Conclusion

This study establishes a human primary cell model that replicates early events in squamous lung carcinogenesis, including abnormal basal cell emergence and molecular changes linked to cancer initiation. Importantly, it demonstrates that AGC kinase inhibition can prevent and reverse these changes, highlighting a promising chemoprevention strategy. This model provides a powerful tool for uncovering early drivers of LUSC, testing therapeutic interventions, and exploring epithelial responses to carcinogens. Next steps include deeper mechanistic studies, expanding donor diversity, and validating additional candidate agents. This work lays the foundation for early intervention approaches in a cancer type with limited treatment options.

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Posters

Group	Title	Authors
1.01	Targeting deregulated SOX2 in early squamous lung cancer - isoform specific inhibition of AKT	Wenrui Guo, Phil Barry, Linsey Porter, Frank McCaughan
1.02	Lung squamous cell carcinoma - from models to prevention	Wenrui Guo, Holly Giles, Alice Chernaik, Namshik Han and Frank McCaughan
1.03	CD47 inhibits clearance of senescent vascular smooth muscle cells and promotes neointima formation	Yee-Hung Chan, Anuradha Kaistha, Jordi Lambert, Sebnem Oc, Kirsty Foote, Nichola Figg, Lauren Kitt, Helle F Jørgensen and Martin Bennett
1.04	Investigation of clonal vascular smooth muscle cell proliferation in humans through combinatorial lineage and identity mapping	Sebnem Oc*, Jordi Lambert*, Krishnaa T. Mahbubani and Helle F. Jorgensen. Sebnem Oc and Jordi Lambert = joint first authorship.
1.05	Characterisation of a Novel Human Cytomegalovirus Restriction Factor and its Viral Evasion	Yuchen Lin, Leah Mary Hunter, Robin Antrobus, Richard Timms, Richard Stanton and Michael Weekes
1.06	Diminished Anti-HCMV T-Cell Functionality in the Elderly: The Role of Checkpoint Pathways	Sarah E. Jackson (1), Rosie Fairclough (1), Veronika Romashova (1), Mahlaqua Noor (1), Y. Eleanor Lim (1), Charlotte J. Houldcroft (1), Robert Doorly (1), Georgina Okecha (1), Claire Atkinson (2), Matthew B. Reeves (2), and Mark R. Wills (1) (1) Department of Medicine, Cambridge Institute of Therapeutic Immunology and Infectious Disease, University of Cambridge School of Clinical Medicine, Cambridge, UK (2) Institute of Immunity and Transplantation, Division of Infection and Immunity, University College London, London, UK
1.07	Novel insights into the HCMV “effectome” from highly multiplexed proteomic analysis of cells expressing individual viral genes	Theo von Wilmowski, Robin Antrobus, Eddie Wang, Richard Stanton and Michael Weekes
1.08	Antagonism of a Novel CRTC-mediated Signalling Pathway by Human Cytomegalovirus	Silvey Xinyue Wang, Marisa Oliveira, Benjamin Ravenhill, Ceri Fielding, Robin Antrobus, Richard Stanton and Michael P. Weekes
1.09	Decoding polygenetic complexity in primary immunodeficiency	Adrià-Arnau Martí Líndez, Sharika Mattoo, Ekaterina Kinnear, Emily Thomas, Katharina Alice Patommel, Rohan Rana, Lauren Tout, Ommar Omarjee, Philippe Dehio, Taco Kuijpers, David Thomas, Paul Lyons, Christoph Hess
1.10	Antagonism of PP2A by HIV-1 Vif enhances spreading infection and syncytia formation in primary human macrophages	Jack A Smith, Pehuén Pereyra Gerber, Sara Marelli, Harriet CT Groom and Nicholas J Matheson

Posters

Group	Title	Authors
1.11	Genetic and immunologic mechanisms of immune-related adverse effects in cancer patients with checkpoint therapy	Yuwei Hao, Anthea Anantharajah, Émeline Favreau, Rochan Chand, Kristy Robledo, Paul Lyons, Martin Stockler, Michelle Cummins, Sonia Yip and Matthew Cook
1.12	Protein-Chromatin Interactions in Acute Hypoxia: a Molecular View of the Oxygen Response	Louise Jordon, Chun-Pei Wu, Niek Wit, James Williamson and James Nathan
1.13	Identification of novel HCMV-encoded necroptosis inhibitors	Hanqi Li, Ceri A, Fielding, Claudia Ganzarain, Robin Antrobus, Paul J. Lehner, Richard J. Stanton and Michael P. Weekes
2.01	The mitochondrial deglutarylase ABHD11 is a novel route to target T cell metabolis	Hudson W Coates, Guinevere L Grice, Eleanor Minogue, Randall S Johnson, and James A Nathan
2.02	Identifying new targets in lung squamous cell carcinoma (LUSC) with single cell transcriptomics of in vitro primary patient models	Holly Giles*, Wenrui Guo*, Joanna Xie, Chaozheng Li, Sunil Modi, Daniel Kottmann, Eliza Yonkova, Maria Eleftheriou,Tania Gracia, Suk Jun Lee, Thomas Dennison, Konstantinos Tzelepis, Toby Gurran, Khalid Saeed, Nicola McCarthy, Erica Bello, Namshik Han*, Frank McCaughan* *These authors contributed equally
2.03	Investigating Kidney-Intrinsic Immune Responses in Sepsis-Associated Acute Kidney Injury	Ping-Huang Tsai, Benjamin J. Stewart, Linus Butt, James McCaffrey, Elvis B. Kidzeru, Elena Prigmore, Agnes Oszlanczi, Di Zhou, Elizabeth Tuck and Menna R. Clatworthy
2.04	EROS plays a non-redundant role in CD4+ T cell differentiation	Paige M Mortimer, Emily K Thomas, Esme Nichols, Gereon Eberling, Kassandra Verzygianni, Ashley Smith, Anthony YC Ng, Alexander Robbins, Neelam Panchal, Katherine Harcourt, William M Rae, Gordon Dougan, James C Lee, Claire Booth, John Grainger, Simon Clare, Kenneth GC Smith, Anneliese Speak, Paul A Lyons, Maria Duque Correa, Rachel Lai, Alice Denton and David C Thomas.
2.05	NK cell evasion and exhaustion in the tumour microenvironment	Vincent Zecchini, Yundi Huang, Jia Jhing Sia and Annie Speak
2.06	A novel GCN1-independent activator of the master protein synthesis regulator GCN2	JiaYi (Jessy) Zhu, Giulia Emanuelli, John Skidmore, Nick W Morrell, Stefan J Marciniak

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2.07	Voluntary Running Alters the Bone Marrow Immune Landscape, but Transplantation Does Not Transfer Its Benefit in HFpEF Pathology	Ankur Saini, Amanda Rodgers, Lauren Kitt, Sebnem Oc, Nichola Figg, Olga Sauchanka, Meritxell Nus Chimeno, Helle F. Jorgensen, Murray Clarke, Thomas Krieg, and Ana Vujic
2.08	E-LUSC – from primary airway cells to lung cancer	Alice Chernaik, Holly Giles*, Wenrui Guo*, Namshik Han and Frank McCaughan
2.09	Feasibility, costs and benefits of remapping genome sequences from GRCh37 to GRCh38 in an Inborn Errors of Immunity cohort	Émeline Favreau, Daniel Greene, Ernest Turro and Chris Wallace
2.10	A phenome-wide analysis of BMI-IL6R variant interaction effects	Ichcha Manipur, Emily Horner, Sarah Spencer, James Thaventhiran and Chris Wallace.
2.11	Synergistic Activation of NLRC4 and NLRP3 Inflammasomes in Autoinflammation Driven by NLRC4 Gain-of-Function Mutations	Weidong Jing, Marisa Dilucca, Joseph Boyle, John Wright, Clare Bryant
2.12	Upregulation ofthe NAIP/NLRC4 Inflammasome and Dysregulation of the IL-18 Axis Are AssociatedWith the Onset and Severity of Acute Respiratory Distress Syndrome	Luke Flower, Emilio Vozza, Elisabeth Robinson, Anthong YCK Ng, Eckart De Bie, Neda Farahi, Zhenguang Zhang, Clare Bryant and Charlotte Summers
2.13	HCMV Specific T cell Activation and Immune Responses in Healthy Donor	Veronika Romashova, Georgina Okecha, Sarah E. Jackson and Mark R Wills.
2.14	Hours of use on CPAP is Correlated with Normalisation of Driving Behaviour recorded by Smart Phone-based app	Kieran Lee, Tristan Bekinschtein, and Ian Smith
3.01	Pathophysiological Insights into Post-Traumatic Amnesia in Mild Traumatic Brain Injury: A CENTER-TBI Study	Olivia E. Rowe, Daniel P. Whitehouse, Lindsay Wilson, András Buki, David K. Menon, Virginia F.J. Newcombe, CENTER-TBI Participants and Investigators
3.02	Specialist surgical care systems – and their relevance to patient outcome and experience, learning from an improvement study in the care of chronic subdural haematoma (IMPROVE-CSDH)	Daniel J Stubbs
3.03	Tracking monocyte kinetics in healthy volunteers and patients with inflammatory arthritis	Neda Farahi, Anthony Y.K.C. Ng, Joseph Hutton, Daniel Gillett, Flavia Sunzini, Richard Hohne, Alex Tate, Nicholas G Shenker, Vasti Lotz, Busola Ade-Ojo, Edwin R Chilvers, Jonathan Cavanagh and Charlotte Summers

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3.05	Time to resolution of symptoms and recovery after mild traumatic brain injury	Hamda Hassan, Paul Sagmueller, Simone LaGuardia, Samuel Millward, Daniel P Whitehouse, Sophie Richter, Anne Manktelow, Harry Mee and Virginia Newcombe
3.06	Lifestyle, behavioural and medical risk factors for Staphylococcus aureus colonisation in the community in England, 2016-2023: A cohort study	Beth Blane*, Stephen Kaptoge*, Matthew Walker, Dinesh Aggarwal, Catarina Sousa, Katherine L Bellis, Carmel Moore, Amy McMahon, Catherine Perry, Plamena P Naydenova, Sophia T Girgis, Joe Brennan, , Asha Akram, Lauma Sarkane, Susan Burton, Elisha Johnson, Shannon Duthie, Svetlana Shadrina, Susan Irvine, Mercedesz Juhasz, Jess Middlemiss, Kathy Raven, Rachel Henry, Agnieszka Osmanska, Hannah Dingwall, Róisín M Boggan, Marta Matuszewska, Duncan Ng, Carol Churcher, Ellena Brooks, Annie Fletcher, Emma Fraser, James Groom, Ben Hyatt, Neenu Linson, Benjamin McCarthy, Nashma Thesin Pelamkulangara, Toska Wonfor, David Anderson, Adam S. Butterworth, Emanuele Di Angelantonio, Joan A Geoghegan, Carl A. Anderson, Julian Parkhill, John Danesh, Sharon J Peacock, Ewan M Harrison * joint first authors
3.07	Impact of extracranial injury on recovery after traumatic brain injury: a machine learning analysis	Jamal Esmaily, Daniel Whitehouse, David Menon, Virginia Newcombe, CENTER-TBI Participants and Investigators
3.08	SARS-CoV-2 infection imprints neutralising antibody responses in the absence of vaccination	Rebecca B. Morse*, Adam Abdullahi*, Mark Tsz Kin Cheng*, NIHR BioResource, Rainer Doffinger, Chee Wah Tan, Ravindra K. Gupta * co-first authors
3.09	Integrating transcriptomic with clinical data to discover drivers of disease progression in Sjögren's syndrome	Yasmine El Hajj, Laura Bergamaschi, Elena Pontarini, Michele Bombardieri, Paul Lyons
3.10	Comparison of endothelin-1 levels in human plasma from coronary arteries measured by enzyme linked immunosorbent assay and Olink high-throughput proteomics platform	Majid Anwar, Rhoda E. Kuc, Kat Bullock, George Abraham, Janet J. Maguire, Stephen P Hoole, Diane Proudfoot and Anthony P Davenport

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Exhibitors

This year, we are delighted to welcome our exhibitors,who bring valuable insights, resources, and opportunities to Research Day. Explore what they have to offer at their stands during the breaks and poster sessions.

Cambridge Enterprise

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LifeArc

We are a not-for-profit life science organisation leading the way for change in rare diseases and supporting promising initiatives in global health.

Through our scientific capabilities, translational expertise and partnerships, we ensure great science achieves its potential and reaches patients faster.

Milner Therapeutics Institute: Flagship Pioneering partnership

The Milner Therapeutics Institute launched a new partnership with Flagship Pioneering and Cambridge University Health Partners (CUHP) in 2025. This is the first Flagship partnership in Europe and reflects their vision to work more extensively in the UK following the establishment of Quotient Therapeutics here in Cambridge.

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