

**Cambridge Immunology Forum**  
**Immune Highways: Interconnected Defence Across Organs**

Tuesday 23<sup>rd</sup> September 2025  
Queen's College, Cambridge, UK

**Programme**

08:30 | Registration and refreshments

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09:20 | Welcome/opening

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**Session 1: Chemotaxis and cytokines**

Chair: Milka Sarris, University of Cambridge, UK

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09:30 | Invited Speaker: **Dr Ang Cui** (Mass General Brigham and Harvard Medical School, USA)  
*Dictionary of immune responses to cytokines at single-cell resolution*

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10:10 | Invited Speaker: **Professor Robert Insall** (University College London, UK)  
*Self-generated gradients and secondary attractants – immune cells steering themselves*

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10:50 | Refreshments, posters and meet with exhibitors

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## Session 2: Tissue remodelling

Chair: Brian Ferguson, University of Cambridge, UK

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11:20 | Invited Speaker: **Professor Markus Feurer** (Leibniz Institute for Immunotherapy, Germany)  
*Tissue Regulatory T Cells*

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12:00 | Invited Speaker: **Dr Régis Joulia** (Imperial College London, UK)  
*How mast cells orchestrate and disrupt specialised immune niches in the lungs and beyond*

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12:40 | Sponsored short talk: **Tom Burley**, UK Regional Business Manager, Alamar Biosciences  
*Comprehensive immune profiling with NULISA – an automated ultra-sensitive proteomics platform for biofluids*

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12:50 | Lunch and networking

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## Session 3: Interconnected organs

Chair: Sarah Jackson, University of Cambridge, UK

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14:20 | Invited Speaker: **Dr Virginia Pedicord** (University of Cambridge, UK)  
*What happens in the gut doesn't stay in the gut: gut feelings in distant immune processes*

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15:00 | Invited Speaker: **Dr Joanne Jones** (University of Cambridge, UK)  
*Human Tissue Immunity – and the role of CD8+ T-regulatory Cells*

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15:40 | Refreshments

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## Session 4: Immune cell trafficking

Chair: Adrian Liston, University of Cambridge, UK

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16:10 | Invited Speaker: **Professor Federica Marelli-Berg** (Queen Mary's London, UK)

*T-cell cardiotropism: mechanisms and clinical implications*

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16:50 | Invited Speaker: **Professor Ulrich von Andrian** (Harvard Medical School, USA)

Tissue-specific patterning of microvascular endothelial cells

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17:30 | Meeting close and poster awards

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17:45 | Drinks reception

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18:30 | Conference Dinner (for those who have registered to attend ONLY)

## Poster presentations

### **P.01 Noncanonical Hedgehog signaling through Smoothed controls cytotoxic T cell migration in the tumor microenvironment**

Chrysa Kapeni, University of Cambridge, Cancer Research UK Cambridge Institute, UK;

### **P.02 Sensory innervation suppresses tertiary lymphoid structure formation to promote lung cancer**

Ya-Hsuan Ho, Cancer Neuroscience Laboratory, Francis Crick Institute, United Kingdom,

### **P.03 Neutrophils bound to mast cell granules induce remote damage during early life allergen-induced lung inflammation**

Ciara Campbell, NHLI, Imperial College London, UK.

### **P.04 Natural killer cells mediate the efficacy of conventional therapies in primary and metastatic cancer**

Christabel Boyles, CRUK CI, University of Cambridge, UK

### **P.05 TCR-independent versus -dependent responses in cytotoxic T lymphocytes**

Ross McKenzie, Babraham Institute, Cambridge UK AND University of Cambridge, Cambridge UK

### **P.06 Blocking aberrant translation enhances modified mRNA vaccine responses and reduces off-target immunogenicity**

Joanna Salmon<sup>1</sup>MRC Toxicology Unit, Gleeson Building, University of Cambridge, UK

### **P.07 Group 2 innate lymphoid cells regulate a fibroblast progenitor niche in the exocrine pancreas in homeostasis, inflammation, and neoplasia.**

Thomas Yip, University of Cambridge, CRUK Cambridge Institute, Cambridge, UK

### **P.08 CD8+ T cells are pro-inflammatory, cytotoxic, and clonally expanded in the early stages of fibrosis due to metabolic dysfunction-associated steatohepatitis (MASH)**

Raju Kumar, Barts Liver Centre, Queen Mary University of London, UK

### **P.09 Regulatory T cells and antigen-presenting fibroblasts coordinate immune suppression in the ovarian cancer metastatic niche.**

Julia Moreno-Vicente, University of Cambridge, CRUK Cambridge Institute, UK

### **P.10 Immune cell-stem cell interactions in the generation of central trained immunity**

Oscar Tsai, Department of Physiology, Development, and Neuroscience, University of Cambridge, UK

### **P.11 OX40 signalling in regulatory T cells helps tune local selective pressure in triple negative breast cancer**

Youhani Samarakoon, CRUK Cambridge Institute, University of Cambridge, UK

### **P.12 Immunotherapies for Agro-Industrial Pollutants**

Ty Kannegieter, University of Cambridge, UK

**P.13 L-type voltage-gated Ca<sup>2+</sup> channels control T cell killing via non-canonical Hedgehog signaling**

Flavio Beke, CRUK Cambridge Institute, UK

**P.14 Investigating the mechanisms behind the misdirected immunity in mIVTmRNA**

Edward Simmons Rosello, University of Cambridge, UK **P.15 Acs14 mutation leads to early and fast progressive hearing loss in mice associated with an inflammatory response within the inner ear**

Elisa Martelletti, Wolfson Sensory, Pain and Regeneration Centre, King's College London, Guy's Campus, UK

**P.16 Blood-based inflammation signatures and their associations with neurodegeneration and cognition in Alzheimer's Disease**

Katherine R. Birditt Department of Clinical Neurosciences, University of Cambridge and Cambridge University Hospitals NHS Trust, University of Cambridge, UK AND UK Dementia Research Institute at University of Cambridge, UK

**P.17 Exploring the Role of Vascular–Myeloid Niches in Immunotherapy Response in Oesophageal Cancer**

Elsita Jungkurth, University of Oxford, UK

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## Poster abstracts

### **P.01 Noncanonical Hedgehog signaling through Smoothened controls cytotoxic T cell migration in the tumor microenvironment**

Chrysa Kapeni<sup>1</sup>, Louise O'Brien<sup>1</sup>, Dilyara Sabirova<sup>1</sup>, Oliver Cast<sup>1</sup>, Sarah McDonald<sup>2</sup>, Kate Fife<sup>1,3</sup>,  
Maike de la Roche<sup>1</sup>

<sup>1</sup>University of Cambridge, Cancer Research UK Cambridge Institute, UK; <sup>2</sup> Histopathology Department, Cambridge University Hospitals NHS Foundation Trust, UK; <sup>3</sup> Oncology Department, Cambridge University Hospitals NHS Foundation Trust, UK

The Hedgehog (Hh) signaling pathway is aberrantly regulated in cancer. Hh inhibitors are successful in treating basal cell carcinoma (BCC) and Sonic Hedgehog–driven medulloblastoma but have largely failed in clinical trials of other solid cancers. We show that Hh inhibitor treatment specifically diminishes CD8 T cell migration into the tumor microenvironment, both in murine cancer models and resected BCCs from patients treated with the Smoothened (Smo) inhibitor vismodegib. Using small-molecule antagonists and genetic knockout models of key Hh signaling components, we demonstrate that the migration defect is mediated exclusively by the signal transducer Smo and not Hh ligands or Gli transcription factors. Smo acts noncanonically as a G protein–coupled receptor to regulate the migration of murine and human CD8 T cells via RhoA. Our data establish a link between Hh inhibition *in vivo* and the antitumor immune response and provide the basis for improved Hh targeting approaches for patients with cancer.

### **P.02 Sensory innervation suppresses tertiary lymphoid structure formation to promote lung cancer**

Ya-Hsuan Ho<sup>1</sup>, Giacomo Bregni<sup>1</sup>, Paola Peinado<sup>1</sup>, Marco Stazi<sup>1</sup>, Pei-Hsing Chen<sup>2</sup>, Claudio Ballabio<sup>1</sup>, Victoire Boulat<sup>3</sup>, Christoforos Tsantoulas<sup>1</sup>, Henrique Veiga-Fernandes<sup>4</sup>, Charles Swanton<sup>5</sup>, Min-Shu Hsieh<sup>6</sup>, Maksym Kopanitsa<sup>1</sup>, George Kassiotis<sup>7</sup>, Isaac M. Chiu<sup>8</sup>, Dinis Pedro Calado<sup>3</sup>, Jin-Shing Chen<sup>2</sup>, Michael-Bogdan Margineanu<sup>1</sup>, Leanne Li<sup>1</sup>

<sup>1</sup> Cancer Neuroscience Laboratory, Francis Crick Institute, United Kingdom, <sup>2</sup> Division of Thoracic Surgery, Department of Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taiwan, <sup>3</sup> Immunity and Cancer Laboratory, Francis Crick Institute, United Kingdom, <sup>4</sup> Immunophysiology Group, Champalimaud Foundation, Portugal, <sup>5</sup> Cancer Evolution and Genome Instability Laboratory, Francis Crick Institute, United Kingdom, <sup>6</sup> Department of Pathology, National Taiwan University Hospital, Taiwan, <sup>7</sup> Retroviral Immunology Laboratory, Francis Crick Institute, United Kingdom, <sup>8</sup> Department of Immunology, Harvard Medical School, USA.

Sensory innervation is crucially involved in pulmonary physiology and pathology, yet its role in lung cancer remains largely unknown. Using mouse models of lung adenocarcinoma (LUAD), we found that tumour progression leads to locally increased innervation and sensory activation. Calcitonin gene-related peptide (CGRP), a major sensory neuropeptide, signals to Ramp1<sup>high</sup>, TNF $\alpha$ <sup>+</sup> macrophages and suppresses the ability of CXCL13<sup>+</sup> fibroblasts to assemble tertiary lymphoid structures (TLS). Local sensory denervation promotes TLS formation, increases production of anti-tumour antibodies, and suppresses LUAD growth. These effects are also recapitulated by pharmacological CGRP antagonism. Cigarette smoke extract further activates nociceptive sensory neurons to accelerate LUAD progression, which can be ameliorated by chemogenetic sensory inhibition. Our findings reveal a previously unappreciated link between nociceptive sensory neurons, TLS, and LUAD, and uncover a novel mechanism by which smoking promotes LUAD tumorigenesis that is independent of somatic mutagenesis.

### **P.03 Neutrophils bound to mast cell granules induce remote damage during early life allergen-induced lung inflammation**

Ciara Campbell, Ekhlas Rahman, Anastasia Voitovich, Minerva Garcia Martín, Simone Walker, Laura Yates, Sejal Saglani, Clare Lloyd, Régis Joulia

NHLI, Imperial College London, UK.

Allergic asthma is common during childhood, and while the association with inflammation and lung dysfunction is well established, how immune cells can mediate distant damage remains unexplored. Mast cells (MCs) and neutrophils are central effector cells in the pathophysiology of allergic airways diseases (AAD) in adults, however their importance during allergic asthma in early life remains to be investigated.

Using a neonatal mouse model of allergic inflammation, 7-day old pups were exposed to 3 intranasal doses of house dust mite (HDM) per week for 3 weeks. Precision cut lung slices (PCLS), light sheet and high-resolution confocal microscopy were employed to investigate the interaction between MCs and neutrophils during early life AAD.

We observed that, in HDM-treated mice, MCs were highly activated, indicated by the presence of extracellular MC granules. Interestingly, these granules were not only present in large airways, the primary site of MC residency, but also in distant areas of the lung parenchyma, where we observed a reduction in vascular perfusion. Mechanistically, we found that MC granules could bind to motile leukocytes such as neutrophils potentially via integrins and Ly6G dependent mechanism.

In summary, our data provides for the first time a mechanism by which MC can spread inflammation via the secretion of granules and co-operate with neutrophil to mediate remote damage during early life. The latter suggests short- and long-term detrimental effects on lung function but also potential remote damage in other organs.

Funded by the BHF and the Wellcome Trust.

### **P.04 Natural killer cells mediate the efficacy of conventional therapies in primary and metastatic cancer**

Christabel Boyles, Shaun Png, Oliver Cast, Julia Moreno-Vicente, Charlotte Simpson, Martin Miller, Michael Gill, James Brenton, and Timotheus YF Halim, \*.

CRUK CI, University of Cambridge, UK

Despite advances in personalised medicine and immunotherapy the standard of care for many cancer patients remains chemo- or radiotherapy. Crucially, the efficacy of these therapies hinges on immune function. While priming of adaptive CD8 T cells can mediate anti-tumour immune responses after conventional therapy, the relative importance of innate natural killer (NK) cells remains unclear. Using orthotopic mouse models we demonstrate that NK cell function contributes significantly to either chemo- or radiotherapy mediated control of ovarian cancer or lung metastases, respectively. Moreover, we assessed the effects of chemotherapy on endogenous tissue-resident immunity at sites of metastatic seeding, which revealed localised NK cell engagement. Using multi-omic single-cell and spatial approaches we infer how carboplatin modulates the metastatic niche. Using IL-15/IL-15R $\alpha$  therapy, we dynamically enhanced the local density of tumour-infiltrating cytotoxic lymphocytes, including NK cells and CD8 T cells, which significantly improved chemotherapy efficacy in models of metastatic ovarian cancer. Our work illustrates a significant and specific contribution of NK cells towards the efficacy of conventional cancer therapy, although local densities of cytotoxic lymphocytes

are crucial for this effect. Relatively safe immunotherapies that broadly enhance tissue-resident innate and adaptive immunity therefore represent an attractive target to improve standard cancer therapy.

### **P.05 TCR-independent versus -dependent responses in cytotoxic T lymphocytes**

Ross McKenzie<sup>1, 2</sup>, Arianne Richard<sup>1</sup>

<sup>1</sup> Babraham Institute, Cambridge UK, <sup>2</sup> University of Cambridge, Cambridge UK

“Bystander”, or TCR-independent, activation of effector and memory CD8+ cytotoxic T lymphocytes (CTLs) has been observed in a variety of inflammatory niches and likely forms a key part of early defence to infection. Traditionally we think of CTLs activating when antigen is presented on the MHC class I of target cells, facilitating recognition by the TCR and induction of effector responses including secretion of cytokines and programmed death of the target via delivery of lytic granules. Increasing evidence indicates that in addition to this TCR-dependent activation, CTLs can also be activated in a TCR-independent manner through innate-associated receptors such as NKG2D or cytokines. Despite decades passing since the observation that IL-12 and IL-18 induce CTL IFN- $\gamma$  secretion, there remain gaps in our understanding of how stimulation with these cytokines intersects with TCR-induced signalling pathways.

Using a combination of live cell imaging, flow cytometry and cytokine secretion measurements, we observed that treatment of CTLs with IL-12 and IL-18 led not only to increased IFN- $\gamma$  secretion and but also CTL clustering. However, cytokine stimulation failed to induce cytotoxic activity against tumour target cells, highlighting that the signalling pathways leading to these different effector functions are separable. Further examination of effects on the transcriptome, chemotaxis and adhesion, alongside activation of signalling mediators, will help elucidate how TCR signalling pathways and those stimulated by IL-12 and IL-18 converge and diverge. Understanding the differences between TCR-dependent and TCR-independent activation will aid design of CAR-T therapies and T cell vaccine technology and understanding of autoimmune reactivity.

### **P.06 Blocking aberrant translation enhances modified mRNA vaccine responses and reduces off-target immunogenicity**

Maria Rust<sup>1\*</sup>, Edward Simmons-Rosello<sup>1\*</sup>, Joanna Salmon<sup>1\*</sup>, Alexander Ferreira<sup>1\*</sup>, Juan Carlos Yam-Puc<sup>1</sup>, Isobel D. Ramsay<sup>2,3</sup>, Thomas E. Mulrone<sup>1</sup>, Pehuén Pereyra-Gerber<sup>2,3</sup>, Wiktoria Parol<sup>1</sup>, Mark Southwood<sup>1</sup>, Munetomo Takahashi<sup>1</sup>, Barbara Kronsteiner-Dobramysl<sup>4</sup>, James Austin<sup>6</sup>, Susan Dobson<sup>6</sup>, Ivan Y. Ji<sup>1</sup>, Nicholas N. Provine<sup>4</sup>, Michael Chapman<sup>1</sup>, Mark Smales<sup>5</sup>, Tobias von der Haar<sup>5</sup>, Lance Turtle<sup>6</sup>, Susanna Dunachie<sup>4,7</sup>, Paul Klenerman<sup>7,8</sup>, Paul Lehner<sup>2,3</sup>, Nicholas J. Matheson<sup>2,3,9</sup>, Anne E. Willis<sup>1</sup>, and James E. D. Thaventhiran<sup>1</sup>

<sup>1</sup> MRC Toxicology Unit, Gleeson Building, University of Cambridge, UK, <sup>2</sup> Cambridge Institute for Medical Research, University of Cambridge, UK, <sup>3</sup> Department of Medicine, University of Cambridge, UK, <sup>4</sup> NDM Centre for Global Health Research, Nuffield Department of Medicine, Centre for Tropical Medicine and Global Health, University of Oxford, UK, <sup>5</sup> School of Biosciences, University of Kent, UK, <sup>6</sup> HPRU in Emerging and Zoonotic Infections, Institute of Infection, Veterinary and Ecological Sciences, Dept of Clinical Infection, Microbiology and Immunology, University of Liverpool, UK, <sup>7</sup> NIHR Oxford Biomedical Centre, Oxford University Hospitals NHS Foundation Trust, UK, <sup>8</sup> Translational Gastrointestinal and Liver Unit, Nuffield Department of Medicine, University of Oxford, UK, <sup>9</sup> NHS Blood and Transplant, Cambridge, UK

N1-methylpseudouridine (1-methyl $\Psi$  or U\*)-modified mRNAs present a revolutionary therapeutic platform. Their drug-development speed and versatility can rapidly deliver new treatments, as demonstrated by the contribution of modified-mRNA vaccines to ending the COVID-19 pandemic. The

sequence code that enables this flexibility, 1-methylΨ-mRNA, is translated by the patient's cells into a therapeutically active protein or, in the case of vaccines, an immune-stimulating peptide-antigen. However, we have shown that 1-methylΨ also promotes frameshifting, generating unintended peptides and off-target immune responses, which may compromise the safety of future therapies. Here we show that the generation of +1-reading frame encoded antigens are associated with inflammation, cell death and cytotoxic CD8 T cell killing. Upon repetitive dosing, these unwanted responses reduce vaccine efficacy as measured by neutralisation titre, germinal centre B cells and antigen specific B cells. Excitingly, we have discovered strategies to prevent the generation of frameshifted antigens leading to an improved in frame vaccine response. We are now assessing the implications of +1-frame encoded antigens in an mRNA therapeutic context where multiple doses are given over a shorter timeframe. Together, this highlights the necessity to screen for +1-frame encoded antigens in new mRNA vaccines and therapeutics, as well as designing strategies to prevent frameshifting from occurring. Our findings therefore pave the way for developing more effective mRNA therapeutics, while reducing the risk of harmful off-target immune responses.

### **P.07 Group 2 innate lymphoid cells regulate a fibroblast progenitor niche in the exocrine pancreas in homeostasis, inflammation, and neoplasia.**

Thomas Yip<sup>1</sup>, Julie Stockis<sup>1</sup>, Shwetha Raghunathan<sup>1</sup>, Charlotte Simpson<sup>1</sup>, Sydney N. Hummel<sup>1</sup>, Julia Moreno-Vicente<sup>1</sup>, Gianmarco Raddi<sup>1</sup>, Celine Garcia<sup>1</sup>, Rugile Linkute<sup>1</sup>, Silvain Pinaud<sup>1</sup>, Hans-Reimer Rodewald<sup>2</sup>, Andrew N. J. McKenzie<sup>3</sup>, Sophie Acton<sup>4</sup>, Patrick Seale<sup>5</sup>, Timotheus Y. F. Halim<sup>1</sup>

<sup>1</sup> University of Cambridge, CRUK Cambridge Institute, Cambridge, UK, <sup>2</sup> Division of Cellular Immunology, German Cancer Research Center; Heidelberg, Germany, <sup>3</sup> MRC laboratory of Molecular Biology, Cambridge, UK, <sup>4</sup> Stromal Immunology Group, MRC Laboratory for Molecular Cell Biology, University College London, London, UK, <sup>5</sup> Institute for Diabetes, Obesity and Metabolism, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA.

**Background:** Group 2 Innate Lymphoid Cells (ILC2s) are tissue-resident innate immune cells critical in orchestrating type-2 immune responses, and reside in mesenchymal niches in close contact with fibroblasts. Recent studies have described a pan-organ hierarchical organisation of the fibroblast lineage. Here, we profiled ILC2s of the exocrine pancreas, and investigated ILC2-fibroblast crosstalk in homeostasis, acute pancreatic inflammation, and cancer.

**Methods:** Naïve, inflamed, and neoplastic pancreata were profiled by flow cytometry, histology, or multiplex immunofluorescence imaging. We assessed two-way communication between ILC2s and fibroblasts using in silico analysis of single-cell and bulk transcriptomic data. Putative crosstalk mechanisms were tested with in vitro and in vivo assays.

**Results:** ILC2 numbers were strongly correlated with fibroblast abundance in homeostasis, and imaging studies showed that most ILC2s co-localise with I133+ fibroblasts within the pancreatic interstitium. Single-cell transcriptomic analysis revealed distinct Pi16+I133+Ly6c1+ and Col15a1+I133-Ly6c1- pancreatic fibroblast populations; using computational inference and experimental lineage-tracing models, we found that Pi16+ fibroblasts represent an interstitial fibroblast progenitor population that can differentiate into Col15a1+ intraparenchymal fibroblasts. In acute pancreatitis, while ILC2-mediated regulation of steady-state fibroblast abundance augments tissue damage, activated ILC2s also promote early proliferation of progenitor Pi16+ fibroblasts that replenish the depleted Col15a1+ fibroblast population. This ILC2-Pi16+ fibroblast axis is dysregulated in pancreatic cancer, resulting in the expansion of a peritumour fibro-immune niche during early tumour development that serves as a source of cancer-associated fibroblasts.

Conclusion: Pancreatic ILC2 inhabit an interstitial fibroblast progenitor niche and enforce homeostatic circuits that regulate steady-state, inflammatory, and cancer associated fibroblast densities.

**P.08 CD8+ T cells are pro-inflammatory, cytotoxic, and clonally expanded in the early stages of fibrosis due to metabolic dysfunction-associated steatohepatitis (MASH)**

Raju Kumar<sup>1</sup>, Wenhao Li<sup>1</sup>, John Loy<sup>2</sup>, Kalpana Devalia<sup>2</sup>, Adam Goralczyk<sup>2</sup>, Humza Malik<sup>2</sup>, Louisa James<sup>3</sup>, Federica Marelli-Berg<sup>4</sup>, Prakash Ramachandran<sup>5</sup>, James Boot<sup>3</sup>, Paul Stevens<sup>3</sup>, Eva Wozniak<sup>3</sup>, Chaz Mein<sup>3</sup>, Robert D. Goldin<sup>6</sup>, William Alazawi<sup>1\*</sup>

<sup>1</sup>Barts Liver Centre, Queen Mary University of London, <sup>2</sup>Bariatric Surgery Unit, Homerton University Hospital, London, <sup>3</sup>Blizard institute, Queen Mary University of London, <sup>4</sup>William Harvey Research Institute, Queen Mary University of London, <sup>5</sup>Centre for Inflammation Research, Institute for Regeneration and Repair, University of Edinburgh, <sup>6</sup>Department of Metabolism, Digestion and Reproduction, Imperial College London

\*Corresponding author

Background and Aims:

Metabolic dysfunction-associated steatohepatitis (MASH) can progress to fibrosis. We previously found an increased number and activation of peripheral blood T cells in patients with MASH compared to steatosis and healthy controls. However, clonality and activation status of T cells in early stages of MASH fibrosis remain unclear and may give unique insights into pathogenesis. Here, we characterised the phenotype and T cell receptor repertoire of T cells in blood, liver, and adipose tissue sampled simultaneously from patients ranging from healthy to non-cirrhotic fibrosis.

Methods:

We performed CITE-seq and TCR sequencing on CD45+ immune cells from liver, subcutaneous (SAT), visceral adipose tissue (VAT), and peripheral blood (PBMC) of 19 MASLD patients (F0-F3 fibrosis) and one healthy control. Histology was assessed using NASH CRN criteria.

Results:

TCR sequencing revealed progressive TCR diversity loss and increased clonal expansion from health to MASLD with fibrosis, with expanded clones enriched in different subsets of CD8 T cells (effector memory, cytotoxic, and NK-like). Clonotype tracking demonstrated shared expanded clones across tissues, often targeting non-infectious antigens. Cell-cell interaction analysis identified clonally expanded CD8 T cells as major signal recipients and TAGLN EndoMT-like endothelial cells as dominant senders in fibrosis. Gene set enrichment of expanded clones in fibrotic tissues showed metabolic rewiring, suppression of exhaustion programs, and tissue-specific signaling, consistent with immunometabolic adaptation.

Conclusions:

Clonal expansion of CD8 T cells with cytotoxic and pro-inflammatory expression profiles occurs early in MASH-related fibrosis and may be a key pathogenic factor in progressive disease

### **P.09 Regulatory T cells and antigen-presenting fibroblasts coordinate immune suppression in the ovarian cancer metastatic niche.**

Julia Moreno-Vicente\*<sup>1</sup>, Thomas Yip<sup>1</sup>, Christabel Boyles<sup>1</sup>, Oliver Cast<sup>1</sup>, Weike Luo<sup>1</sup>, Shaun Png<sup>1</sup>, Julie Stockis<sup>1,2</sup>, Charlotte Simpson<sup>1</sup>, Celine Garcia<sup>1</sup>, Chandra Chilamakuri<sup>1</sup>, Johanna Barbieri<sup>1</sup>, Panagiotis Papadopoulos<sup>1</sup>, Sophie Lucas<sup>2</sup>, Virginia Pedicord<sup>3</sup>, Sophie Acton<sup>4</sup>, Mark Cragg<sup>5</sup>, James Brenton<sup>1</sup>, and Timotheus Y.F. Halim<sup>1</sup>.

<sup>1</sup> University of Cambridge, CRUK Cambridge Institute, UK; <sup>2</sup> de Duve Institute, Belgium; <sup>3</sup> University of Cambridge, Department of Medicine, UK; <sup>4</sup> University College London, UK; <sup>5</sup> University of Southampton, UK.

**Background:** High-grade serous ovarian cancer (OC) is the most lethal gynecological cancer and remains largely unresponsive to immunotherapies. Here, we uncover a multi-layered crosstalk between immune and stromal cells in early omental metastases that dictates OC progression.

**Methods:** We investigated the cellular composition of early omental metastases with an in vivo proximity-labelling method, coupled with high-parameter flow cytometry and bulk RNA sequencing, to identify molecular drivers of metastasis. We developed new transgenic mouse models and tested novel immunotherapies to interrogate the mechanisms that impair anti-tumour immunity.

**Results:** Fibroblasts and mesothelial cells were found near disseminating tumour cells, with MHC-II<sup>+</sup> antigen-presenting cancer-associated fibroblasts (apCAF) expanding in early metastases. Transcriptional analysis of tumour-neighbouring apCAF revealed enrichment in epithelial-to-mesenchymal transition and immune-regulatory genes. In parallel, regulatory T cells (Treg) also accumulated in early metastases, and transient depletion abrogated tumour growth. We then confirmed direct interaction between both cell types via in vivo substrate transfer using novel Treg-specific LIPSTIC mice. Functionally, fibroblast-specific MHC-IIKO mice revealed impaired Treg function, albeit the primary effect was a marked reduction in CD4 T-cell proliferation and function. Blocking antibodies targeting upregulated pathways in tumour-neighbouring apCAF or agonistic stimulation of CD4 T cells similarly reduced Treg suppression, decreased tumour burden and led to long term anti-tumour immunity.

**Conclusion:** Tregs suppress the formation of anti-tumour immunity during early OC metastasis. Antigen-presenting CAF engage in a multi-layered crosstalk with Tregs and CD4 T cells that controls metastasis growth, and targeting these interactions offers new therapeutic avenues for OC.

### **P.10 Immune cell-stem cell interactions in the generation of central trained immunity**

Oscar Tsai, Elijah Cui, Salik Borbora, Milka Sarris

Department of Physiology, Development, and Neuroscience, University of Cambridge, UK

In trained innate immunity, a primary insult trains innate immune cells, long thought to have no memory capacity, to respond differentially to a secondary infection. In contrast to the genetic changes in classical adaptive immunity, trained innate immunity has been attributed to metabolic and epigenetic changes in hematopoietic stem cells. The signals and interactions that govern these changes are poorly understood. Embryonic zebrafish (*Danio rerio*) are useful model organisms to study the generation of innate immune memory due to their transparency and lack of adaptive immunity. Previous work in the lab has shown primary infection with nonpathogenic *Escherichia coli* in the otic vesicle induces trained immunity, protecting against mortality in secondary *Pseudomonas aeruginosa* infection.

To interrogate hematopoietic stem cell interactions during the generation of trained innate immunity, live imaging of innate immune cell-stem cell interactions was performed in the caudal hematopoietic tissue in zebrafish embryos at 24-48h after *E. coli* challenge.

We found that neutrophil-stem cell interactions occurred after *E. coli* challenge, however were not significantly changed as compared to control PBS challenge, while macrophage-stem cell interactions were significantly increased. These increased macrophage-stem cell interactions lasted longer, as well as resulting in increased engulfment of the stem cell by the macrophage.

These findings indicate *E. coli* training challenge alters macrophage-stem cell interaction. Macrophage-stem cell interactions have been shown to maintain hematopoietic stem cell function. Future studies will attempt to elucidate the effects of immune stimulants on hematopoietic stem cell clonality, selection, and immune cell generation.

### **P.11 OX40 signalling in regulatory T cells helps tune local selective pressure in triple negative breast cancer**

Yuhani Samarakoon<sup>1</sup>, Fanourios Georgiades<sup>1</sup>, Stela Monk<sup>1</sup>, Salmaan Ahmed<sup>1</sup>, Julie Stockis<sup>1</sup>, Walid Khaled<sup>1</sup>, Raza Ali<sup>1</sup>, Marc Cragg<sup>2</sup>, Tim Halim<sup>1</sup>,

<sup>1</sup>CRUK Cambridge Institute, University of Cambridge, UK, <sup>2</sup> University of Southampton

Tumours evolve from benign lesions under constant surveillance by the adaptive immune system. While cytotoxic CD8+ T cells exert selective pressure, the role of CD4+ regulatory T cells (Tregs) on immunoediting remains ambiguous. We hypothesize that the co-stimulatory receptor OX40 (Tnfrsf4) controls tissue-resident Treg responses via local innate-adaptive immune circuits in pre-neoplastic lesions that orchestrate tolerance to emerging neoepitopes. Temporal deletion of OX40 on Tregs (OX40(del)Treg) in a model breast cancer evolution (MMTV-PyMT;Foxp3CreERT2;Tnfrsf4fl/fl) changes the immune landscape of tumour lesions. These lesions have greater proportions of effector CD8+, conventional T cells and NK cells. Mice bearing OX40(del)Treg predominantly presented with non-palpable early tumour lesions at endpoint, whereas mice with OX40(wt)Treg presented with palpable lesions. Deletion of OX40 on Tregs greatly reduced tumour incidence and is a survival advantage in TNBC. Ongoing work focuses on further charactering the molecular details of this survival advantage and reevaluating methods of targeting OX40 in preclinical breast cancer models.

### **P.12 Immunotherapies for Agro-Industrial Pollutants**

Ty Kannegieter, James Thaventhiran

University of Cambridge, UK

Agro-industrial chemicals (e.g. pesticides, surfactants, plasticizers) provide tremendous utility to modern society. However, some of these chemicals cause severe health consequences following acute and/or chronic exposure. Acute pesticide poisoning alone afflicts some 25,000,000 people, killing more than 200,000 of them, annually. With few exceptions, there are limited interventions to prevent these toxic events beyond banning chemical use – which can itself have tremendous negative impacts on public health.

Here, we propose a method by which to prevent the toxicities at the patient level via use of immunotherapeutics. Predicated upon a rich literature of immunotherapies for substance use disorder (SUD), we hope to demonstrate that similar design methodologies may be applied to agro-industrial targets.

To date, we have demonstrated the ability to elicit immune responses specific to 5 diverse chemicals which are or have been of extreme significance to global agro-industrial production - 2,4D, Atrazine, Paraquat, DDT, and Chlorpyrifos. These molecules have known or highly suspected acute and chronic toxicities. Here, we provide overviews of immunotherapy design, development, and testing. Data ranges from structural confirmation of immunogens to a distributional “challenge trial” which models real-world toxicity in vivo.

Demonstration that diverse persistent organic pollutants can be targeted and mollified via immunotherapy use, we hope, would support an expansion of what we, as an immunological community, see as a druggable target. This may imply a broadening of immunotherapies from targeting the biotic and viral to also targeting xenobiotic threats.

### **P.13 L-type voltage-gated Ca<sup>2+</sup> channels control T cell killing via non-canonical Hedgehog signaling**

Flavio Beke, Joachim Hanna, Chrysa Kapeni, Louise M. O'Brien, Valentina Carbonaro, Nico Mueller, Chandra Chilamakuri, Maike de la Roche

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Cytotoxic CD8<sup>+</sup> T lymphocytes (CTLs) efficiently eliminate infected and cancerous cells throughout the body. Hedgehog signaling is critical for CTL-mediated killing. Remarkably the pathway cannot be induced canonically by extracellular Hedgehog ligands but instead is activated by the T cell receptor (TCR). How the Hedgehog pathway is mechanistically activated downstream of the TCR is unknown. Here we show that L-type voltage gated Ca<sup>2+</sup> (Cav1) channels at the plasma membrane downstream of the TCR control an extracellular Ca<sup>2+</sup> influx leading to induction of the Hedgehog transcription factor Gli1 which is essential for efficient CTL killing in vitro and in vivo. This novel non-canonical Hedgehog pathway is independent of canonical signaling and represents a primary mechanism of Gli1 induction in naïve CD8<sup>+</sup> T cells, while CTLs can also activate Gli1 via MAPK. We show that Cav1 channel-controlled Gli1 induction is functionally required for CTL killing in mice and humans and other cytotoxic lymphocytes. Importantly, we demonstrate that killing capacity can be amplified using a small molecule Cav1 channel agonist or by overexpression of a gain-of-function Cav1 subunit. Our findings indicate that Gli inhibitors, currently in clinical trials as anti-cancer therapeutics, likely inhibit the cytotoxic anti-tumor response. On the other hand, our work opens up the possibility to enhance CTL performance in the clinic by selectively increasing Ca<sup>2+</sup> flux via Cav1 channels, for example in the context of CAR T cell therapy.

### **P.14 Investigating the mechanisms behind the misdirected immunity in mRNA**

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The COVID-19 pandemic showcased the remarkable potential of mRNA technology in combating infectious diseases. Its speed, adaptability, and scalability are now being harnessed across many therapeutic pipelines. However, we have shown that the N1-methylpseudouridine (1-methyl $\Psi$ ) modification, central to the success of this technology, can also contribute to misdirected CD8<sup>+</sup> T-cell immunity through the production of unintended, mistranslated peptides. This poses a significant challenge for mRNA-based therapeutics, as any unintended CD8<sup>+</sup> T-cell response is a cause for concern. Specifically, we identify two translation-level mechanisms acting together to drive this mistranslation: +1 ribosomal frameshifting and stop codon readthrough. Together, these processes lower translational fidelity, producing novel antigenic peptides capable of eliciting immune responses distinct from those intended. We further show that certain design features of the Pfizer-BioNTech BNT162b2 vaccine and other mRNA sequences can inadvertently promote these effects, illustrated by the relative inefficiency

of the UGA stop codon in preventing mistranslation. Finally, we present an optimisation strategy that mitigates mistranslation while preserving the translational benefits of 1-methyl $\Psi$  incorporation. Our findings reveal key molecular drivers of misdirected immunity following mRNA vaccination and provide a framework for designing next-generation mRNA vaccines with enhanced safety, potentially improving both therapeutic efficacy and long-term outcomes.

### **P.15 Acsl4 mutation leads to early and fast progressive hearing loss in mice associated with an inflammatory response within the inner ear**

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Acyl-CoA synthetase long-chain family member 4 (Acsl4) is a key enzyme in lipid metabolism within the arachidonic acid cascade, a central pathway regulating inflammation and its resolution. Here, we investigated the impact of Acsl4 mutation on auditory function and the role of cochlear immunity in hearing loss.

We generated Acsl4 conditional knockout mice using Sox10-Cre to delete exon 5 in the inner ear. Acsl4 mutant mice had normal auditory thresholds at 2 weeks of age but rapidly lost hearing sensitivity within a week, starting with high frequencies. By 4 weeks, thresholds were severely elevated across all frequencies. Histological analyses revealed degeneration of hair cell stereocilia, loss of sensory hair cell nuclei, and reduced ribbon synapses in surviving hair cells.

To assess immune responses within the cochlea (inner ear), we performed flow cytometry at 3 weeks, after the onset of hearing loss. Acsl4 mutants displayed increased numbers of leukocytes and myeloid immune cells in the cochlea. In parallel, cochlear macrophages in mutants adopted an ameboid, activated morphology along the cochlear duct, contrasting with the extensively dendritic, resting morphology observed in controls. In contrast, preliminary analyses at 2 weeks, prior to hearing loss, showed no significant differences in macrophage morphology between mutants and controls. RT-qPCR showed upregulation of pro-inflammatory cytokines and chemokines, including TNF- $\alpha$ , Ccl2, and Ccl5, at 3 weeks, coinciding with immune infiltration and morphological activation.

Overall, these findings indicate that Acsl4 mutation causes a rapidly progressive hearing loss accompanied by changes in cochlear immune responses.

### **P.16 Blood-based inflammation signatures and their associations with neurodegeneration and cognition in Alzheimer's Disease**

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Immune signalling alterations are increasingly implicated in Alzheimer's disease (AD), yet the complexity and heterogeneity of cytokine changes across the disease spectrum remain underexplored. This study examined plasma cytokine profiles in individuals on the AD spectrum and healthy controls, using data from the diverse, population-representative Global Alzheimer Platform Bio-Hermes study.

We analysed 176 participants with amyloid-positive AD-dementia (n=84) or mild cognitive impairment (MCI, n=92), and 173 age- and sex-matched healthy controls with amyloid-negative biomarkers. Thirty-seven cytokines were measured using a Luminex panel. Principal component analysis (PCA) with varimax rotation was used to reduce dimensionality, and outliers were excluded using Mahalanobis distance. PCA components were compared across diagnostic and racial groups. Associations with p-tau217 (pathology), neurofilament light (NfL; neurodegeneration), and Mini-Mental State Examination (MMSE; cognition) were tested using robust regression. Structural equation modelling (SEM) assessed direct and indirect cytokine effects on MMSE.

Two components were identified: PC1 (generalised inflammatory dysregulation; IL-16, TNF-RII, CXCL10) and PC2 (proinflammatory cytokines; TNF- $\alpha$ , IL-17A, IL-7). PC1 was elevated in patients vs. controls (p=0.011) and in Black/African American vs. White participants (p=0.042). PC1 correlated with higher NfL (p=0.006), and PC2 with lower MMSE scores (p<0.001), but neither with p-tau217. SEM showed PC2 had a direct negative association with MMSE, while PC1 had an indirect effect via NfL.

These findings reveal two inflammatory signatures linked to neurodegeneration and cognition, differing by diagnosis and race. Blood-based inflammatory profiling may support scalable biomarker development and future experimental medicine in AD.

### **P.17 Exploring the Role of Vascular–Myeloid Niches in Immunotherapy Response in Oesophageal Cancer**

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Immune checkpoint blockade (ICB) efficacy is contingent not only on immune activation but also on the spatial coordination of immune and stromal compartments within the tumour microenvironment (TME). Here, we delineate a temporal model for durable ICB response and identify structural prerequisites for its successful progression.

Using single-cell RNA sequencing from metastatic oesophageal cancer patients treated with neoadjuvant ICB, we stratified tumours by clinical outcome and performed longitudinal cell–cell communication analysis. Responders exhibited a treatment-naïve enrichment of myeloid antigen-presenting cells (APCs), including monocytes and dendritic cells. This population expanded over time, while non-responders lacked sustained APC support.

Critically, only APC-rich tumours underwent vascular remodeling post-ICB, marked by increased pericyte coverage and endothelial maturation; hallmarks of an immune-permissive niche. In contrast, APC-deficient tumours remained structurally inert. CellChat-based interactome mapping revealed that responders recapitulated the signalling architecture of healthy oesophageal tissue, marked by coordinated dialogue between APCs, pericytes, and endothelial cells.

These findings uncover a conserved vascular–myeloid axis that supports immune trafficking and memory formation, implicating inter-organ principles of stromal–immune crosstalk in tumour control. The ability to either pre-condition or reprogram this axis may be a key determinant of ICB success.

Our work contributes to the broader understanding of immune highways and highlights the necessity of integrated stromal–immune architecture in facilitating systemic and localised defence mechanisms across tissues.