CHINESE ACADEMY of MEDICAL SCIENCES OXFORD INSTITUTE

NUFFIELD DEPARTMENT of MEDICINE

UNIVERSITY OF OXFORD

CAMS OXFORD INSTITUTE (COI) NETWORK MEETING 2025 BOOKLET

6th June 2025, OXFORD

DATE

The Network Meeting will take place on Friday, 6th June, 2025 with the following schedule:

08:45 ~ 09:30	Registration and Coffee
09:30 ~ 09:45	CAMS Oxford Institute Update
09:45 ~ 10:45	Scientific Session 1
10:45 ~ 11:10	Flash Talks Session 1
11:10 ~ 11:25	Refreshment Break & Poster Session
11:25 ~ 12:25	Scientific Session 2
12:25 ~ 12:55	Flash Talks Session 2
12:55 ~ 14:30	Lunch and Poster Session
14:30 ~ 15:30	Scientific Session 3
15:35 ~ 15:55	Flash Talks Session 3
15:55 ~ 16:15	Refreshment Break
16:15 ~ 17:20	Scientific Session 4
17:20 ~ 17:30	Closing Remarks & Prize giving
17:30 ~ 18:10	Transport to Ashmolean Museum
18:10 ~ 21:30	Drinks, Dinner and Networking

VENUE

Conference Venue:

Richard Doll Building

Old Road Campus,
Headington, Roosevelt Drive,
Oxford OX3 7LF

Drinks, Dinner & Networking:

The Ashmolean Museum

Beaumont St,
Oxford, OX1 2PH

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Welcome to CAMS Oxford Institute Network Meeting 2025

Tao Dong
Co-Director
CAMS Oxford Institute

Dear all,

It is my pleasure to welcome you all to the 2025 CAMS Oxford Institute Network Meeting.

This event will be a fantastic opportunity for our COI PI's to provide support and advice to our growing cohort of exciting young scientists and students.

2024 and 2025 to date, have been both exciting and challenging within scientific research and administration. There have been many achievements including new awards granted, papers published and platforms strengthened and developed.

The training activities have continued, and we will be delivering the summer school next month in Beijing. The CSC-COI Scholarships have grown, and we look forward to welcoming the next cohort later this year.

We have welcomed our first CAMS-COI Postdoctoral Fellowships, with CAMS researchers joining the network from China, as employees, for the first time.

All of this activity has been assessed by the Trusted Research Office, which have been managing the challenges of the UK Government policy associated with export licence control.

The presentations and talks have been selected from the abstracts submitted to the COI Scientific Strategy Committee, and we hope that the day will highlight the breadth and strength of this growing network. We have ensured there is plenty of time for networking and discussion, so please do make the most of this opportunity throughout the day and the evening event.

I look forward to seeing you all!

Professor Tao Dong
Co-Director of CAMS Oxford Institute

MEETING ITINERARY

6th of June 2025, Richard Doll Building

08:45 ~ 09:30	Registration and Coffee	RDB Reception
09:30 ~ 09:45	CAMS Oxford Institute Update	Prof. Tao Dong Co-Director of COI

09:45 ~ 10:45	Scientific Session 1	Chair: Graham Ogg
09:45 ~ 10:05	Leveraging the power of multimodal spatial profiling to delineate local influences determining immune response to cutaneous squamous cell carcinoma	Matthew Bottomley
10:05 ~ 10:25	Phenotypic, clonal, and spatial deconvolution of CD8+ T cell responses in non-small-cell lung cancer	Adam Bates
10:25 ~ 10:45	Integrative -Omics reveals a dynamic posttranslational modification (PTM) landscape associated with neutrophil differentiation	Andreas Damianou

10:45 ~ 11:10	Flash Talks Session 1	Chair: Christina Heroven
10:45 ~ 10:50	Mapping specificity and cross-reactivity of wild-type and engineered T cell receptors	Kristen Koopmans
10:50 ~ 10:55	Linking Function to Location: Developing a Spatial TCR Sequencing Approach to Study Antigen-Specific T Cells in Tissue	Zinan Yin
10:55 ~ 11:00	Spatial analysis of the chronic hepatitis B and D liver reveals new aspects of viral pathogenesis and cancer.	Nadina Wand; Maria Veretennikova
11:00 ~ 11:05	Immunosuppression drives a skewed chemokine landscape associated with altered T cell infiltration in post-transplant cutaneous squamous cell carcinoma	Girishkumar Kumaran
11:05 ~ 11:10	Comprehensive characterization of tumor-specific CD8 T cells in HR+ breast cancer patients reveal an impaired antitumoral response in patients with lymph node metastasis	Mariana Pereira Pinho

11:10 ~ 11:25 Refreshment Break and Poster Session RDB Atrium

MEETING ITINERARY

11:25 ~ 12:25	Scientific Session 2	Chair: Julian Knight
11:25 ~ 11:45	Context-specific regulatory genetic variation in MTOR dampens neutrophil-T cell crosstalk in sepsis, modulating disease	Ping Zhang
11:45 ~ 12:05	Regulation of viral replication by the cellular oxygen sensing pathway	Peter Wing; Jiyeon Ha
12:05 ~ 12:25	Subsets of regulatory T cells are CD1a-reactive and dysfunctional in psoriasis	Yi-Ling Chen

12:25 ~ 12:55	Flash Talks Session 2	Chair: Nikolaos Kanellakis
12:25 ~ 12:30	CD1a contributes to early bacterial and stress sensing in the skin	Karmella Naidoo
12:30 ~ 12:35	Loop extrusion by cohesin plays a key role in enhancer-activated gene expression during differentiation	Felice Tsang
12:35 ~ 12:40	Multi-Omic Approach Reveals Neutrophil Heterogeneity in Pleural Infection	Yinzhou Feng
12:40 ~ 12:45	Potent and broadly neutralising antibodies against sarbecoviruses elicited by SARS-CoV-2 infection	Aiste Dijokaite-Guraliuc
12:45 ~ 12:50	Neutrophil elastase and NETs contribute to disease exacerbation in pleural infection	Julia Chu
12:50 ~ 12:55	Identifying tumour-cell-intrinsic genes that mediate resistance to T cell recognition and cytotoxicity	Nicole E. Fletcher

12:55 ~ 14:30 Lunch and Poster Session RDB Atrium

14:30 ~ 15:30	Scientific Session 3	Chair: Benedikt Kessler
14:30 ~ 14:50	Induced-Proximity Strategies to Modulate Receptor Signalling in Inflammation and Cancer	Ricardo Fernandes
14:50 ~ 15:10	Computational multistate modeling and immunological synapse analyses reveal bispecific T cell engager quality hierarchy in treating cancers	Tanmay Mitra
15:10 ~ 15:30	Unveiling the Complete Spectrum of SARS-CoV-2 Fusion Stages by In Situ Cryo-ET	Caner Akil

MEETING ITINERARY

15:35 ~ 15:55	Flash Talks Session 3	Chair: Yanchun Peng
15:35 ~ 15:40	Tumour Cells in Transit: Single-Cell Analysis of Lymphatic CTCs in Stage III Melanoma	George Adigbli
15:40 ~ 15:45	Investigating functional effects of integrin expression on SARS-CoV-2 virus-specific CD8+ T cells and their potential impact on pathology	Maya Pidoux
15:45 ~ 15:50	Memory HBx-specific T cells associate with viral control	Guihai Liu
15:50 ~ 15:55	SSX2 Reactive High Functional Avidity TCR for Tumour Adoptive Cell Therapy	Fei Gao
15:55 ~ 16:15 Refreshment Break RDB Atrium		

16:15 ~ 17:30	Scientific Session 4	Chair: E. Yvonne Jones
16:15 – 16:30	Second-generation Lymphoid Organoids for mechanistic studies of human immune regulation.	Pablo F. Céspedes Donoso
16:30 ~ 16:50	Understanding Immunology and Disease Pathogenesis with an Integrated Bioinformatics Platform	Elie Antoun
16:50 ~ 17:05	Oxford University Innovation: supporting researchers, innovation and entrepreneurship at Oxford	Steve Silvey
17:05~ 17:20	From COI to Start-up: Our Journey from Discovery to Company	Ricardo Fernandes
17:20 ~ 17:30	Closing Remarks & Prize giving	Mr. Darren Nash Associate Head of NDM
17:30 ~ 18:10 Travel and Networking		

17:30 ~ 18:10	Transport to Ashmolean Museum	Coach

18:10 ~ 21:30	Dinner and Networking	Ashmolean Museum
18:10 ~ 18:40	Drink Reception	Atrium
19:00 ~ 21:30	Formal Dinner and Entertainment	Greek and Roman Sculpture
21:30	Departure	

MAIN TALKS

Scientific Session 1

Chair: Prof. Graham Ogg

Scientific Session 2

Chair: Prof. Julian Knight

Scientific Session 3

Chair: Prof. Benedikt Kessler

Scientific Session 4

Chair: Prof. E. Yvonne Jones

Leveraging the Power of Multimodal Spatial Profiling to Delineate Local Influences Determining Immune Response to Cutaneous Squamous Cell Carcinoma

Matthew Bottomley

Main Talk

Matthew J Bottomley[1], Michael McKenna[2], Zehua Li[1], Noushin Zibandeh[1], Girishkumar Kumaran[1], Megat Abd Hamid[1], Elie Antoun[1], Eleni Ieremia[3], Lilian Brewer Lisboa[2], Trieu My Van[2], Tao Dong[1], Graham Ogg[1,4]*

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3. *Department of Histopathology, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK*
4. *MRC Translational Immune Discovery Unit, Weatherall Institute of Molecular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, UK*

Abstract

Cutaneous squamous cell carcinoma (CSCC) is the most common metastasising malignancy affecting Caucasian populations. Advanced disease is associated with poor outcomes, with only half of patients responding to current immunotherapy regimens. Robust CD8+ T cell responses play a key role in determining CSCC outcome but understanding of local influences upon CD8+ behaviour within CSCC is limited.

Here we show by multimodal tissue profiling alongside functional validation that TGF-β2 signalling in the setting of local inflammation, is co-opted to promote endothelial trans-differentiation into suppressive cancer-associated fibroblasts, representing a dominant mechanism by which malignant keratinocytes and fibroblasts regulate immune infiltration into fibrovascular niches at the leading tumour edge.

Such niches demonstrate parameters predicting enhanced tumour invasion and immunotherapy resistance. Our results identify pathways which drive tumour invasiveness and exclude infiltrating effector lymphocytes at the tumour edge.

We identify potential targets for therapy to target these niches and improve outcome in advanced disease.

Phenotypic, Clonal, and Spatial Deconvolution of CD8+ T Cell Responses in Non-Small-Cell Lung Cancer

Adam Bates
Dong Group

Main Talk

A. Bates[1,2], Z. Yin[1,2], F. Gao[1,2], J. McCarthy[2], K. Koopmans[2], N. Fletcher[1,2], M. Abd Hamid[2], L. Felce[2], E. Antoun[2], J. L. Chen[2], X. Yao[2], M. Bottomley[2], A. Simmons[1,2], R. Fernandes[2], Y. Peng[1,2], T. Dong[1,2]

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Abstract

Despite recent improvements in diagnosis and treatment, non-small-cell lung cancer remains the leading cause of global cancer-related mortality. Although immune checkpoint blockade can promote durable anti-tumour immune responses in a subset of patients, its limited success has been attributed to uncharacterised heterogeneity within the tumour microenvironment.

Here, we have used paired scRNA/TCR-seq, CITE-seq, and flow cytometry to characterise $CD8^+$ T cells in non-small-cell lung cancer. Our analysis reveals a rare but broadly detectable 'NK-like' $CD8^+$ T cell population defined by a T_{rm} like phenotype, high expression of granulysin, and a unique subset of KIR/KLR germ-line receptors. Clonal and phenotypic analyses indicate that 'NK-like' cells are related to canonically exhausted and actively cycling cells and are distinct from effector-memory-like phenotypes associated with non-tumour-reactive "bystanders". Additionally, 'NK-like' T cells exhibit characteristics of true tumour-infiltrating T cells, defined using NanoString Technologies' GeoMX® Digital Spatial Profiler.

Finally, we demonstrate that the transduction an 'NK-like' TCR into healthy donor-derived $CD8^+$ T cells facilitates TCR:HLA-A*02:01 dependant cytokine secretion and cytotoxicity in response to several cancer cell lines. This broad reactivity likely indicates specificity for a conserved tumour-associated antigen giving this TCR broad therapeutic potential.

Although validation of tumour-reactivity for additional 'NK-like' clonotypes is required, the identification of a non-exhausted, clonally expanded T cell population able to infiltrate and recognise tumours represents an exciting development in our understanding of immuno-oncology. This population may mediate observed responses to NKG2a blockade and may prove to be a therapeutically targetable population for patients unable to respond to current therapies.

This work was supported by the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (CIFMS), China (grant number: 2018-I2M-2-002)

Integrative-Omics Reveals a Dynamic Posttranslational Modification (PTM) Landscape Associated With Neutrophil Differentiation

Andreas Damianou
Kessler Group

Main Talk

Mohammed Akhbor[1], Ananda Kishore Mukherjee[2], Svenja Hester[1], Sarah Flannery[1], Iolanda Vendrell[1], Irina Udalova[2], Benedikt M Kessler[1,3] and Andreas Damianou[1,3]

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2. *Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK*
3. *Chinese Academy of Medical Sciences (CAMS) Oxford Institute (COI), Nuffield Department of Medicine, University of Oxford, OX3 7BN*

Abstract

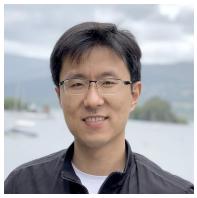
Neutrophils are frontline effectors of the innate immune system, rapidly mobilised in response to both inflammation and microbial invasion. Their development from hematopoietic progenitors is a tightly regulated process involving lineage commitment, functional maturation, and priming for rapid immune responses. Although key transcriptional and signalling pathways involved in neutrophil differentiation have been described, the contribution of post-translational modifications (PTMs)—critical modulators of protein activity, stability, and interactions—remains largely unexplored to date.

Here, we present the first comprehensive, unbiased characterization of global proteomic and PTM dynamics during neutrophil differentiation using state-of-the-art mass spectrometry based proteomics. By applying parallel enrichment strategies for ubiquitinated (di-Gly-modified) and phosphorylated peptides, we quantified over ~6,000 proteins, ~30,000 ubiquitination sites, and ~14,000 phosphorylation events across defined stages of neutrophil development. These datasets reveal stage-specific patterns of PTM regulation, implicating a coordinated remodelling of signalling networks and effector functions during differentiation.

Integrative bioinformatic analyses identified potential candidate master regulators, including previously unrecognised E3 ligases, and deubiquitinases (DUBs), whose activity or modification state strongly correlates with distinct differentiation phases. Several of these hits are currently under experimental validation to assess their mechanistic role in neutrophil lineage specification and function.

Our findings provide a high-resolution dynamic molecular PTM landscape of neutrophil differentiation, highlighting the underappreciated role of protein phosphorylation and ubiquitylation in shaping innate immune cell fate. This work opens new avenues for understanding neutrophil biology and developing strategies to therapeutically modulate immune responses in inflammatory and infectious diseases.

Context-Specific Regulatory Genetic Variation in MTOR Dampens Neutrophil-T Cell Crosstalk in Sepsis, Modulating Disease



Ping Zhang
Knight Group

Main Talk

Ping Zhang[1,2], Patrick MacLean[1], Alicia Jia[1], Callum O'Neill[1], Alice Allcock[1], Ethan Prince[1], Imogen Dyne[1], Kiki Cano-Gamez[1,4], Hanyu Qin[1,2], Chloe Wainwright[1], Giuseppe Scozzafava[1], Andrew Brown[1], James O. J. Davies[5], Amanda Y. Chong[1], Alexander J. Mentzer[1,2], Katie L. Burnham[3], Emma E. Davenport[3], and Julian C. Knight[1,2*]*

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3. *Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, UK.*
4. *Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK*
5. *Medical Research Council Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK.*

Abstract

Sepsis is a heterogeneous clinical syndrome with a high mortality, requiring personalised stratification strategies. Here, we characterise genetic variation that modulates MTOR, a critical regulator of metabolism and immune responses in sepsis.

The effects are highly context specific, involving a regulatory element that affects MTOR expression in activated T cells with opposite direction of effect in neutrophils.

We show that the G-allele of the lead variant, rs4845987, associated with decreased risk of T2D, reduces MTOR expression in T cells and improves survival in sepsis patients due to pneumonia, with effects specific to sepsis endotype.

Using ex vivo models, we demonstrate that activated T cells promote immunosuppressive sepsis neutrophils through released cytokines, a process dampened by hypoxia and the mTOR inhibitor rapamycin.

Our work demonstrates a novel epigenetic mechanism that fine-tunes MTOR transcription and T cell activity via the variant-containing regulatory element, which exhibits an allelic effect upon vitamin C treatment.

These findings reveal how genetic variation interacts with disease state to modulate immune cell-cell communication, providing a patient stratification strategy to inform more effective sepsis treatment.

Regulation of Viral Replication by the Cellular Oxygen Sensing Pathway

Jiyeon Ha

Peter Wing

Wing Group

Main Talk

Jiyeon Ha[1], Parul Sharma [2], Sammi Ta[3], James M. Harris[3], Eleanor Bentley[2], Adam Kirby[2], Daniele Mega[2], David A. Matthews[4], Peter Balfe[3], Jan Rehwinkel[5], Anja Kipar[2,6], James P. Stewart[2+], Jane A. McKeating[1,3], Peter A.C. Wing[1]

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5. *Medical Research Council Translational Immune Discovery Unit, Medical Research Council Weatherall Institute of Molecular Medicine, Radcliffe Department of Medicine, University of Oxford, UK*
6. *Laboratory for Animal Model Pathology, Institute of Veterinary Pathology, Vetsuisse Faculty, University of Zurich*, Winterthurerstrasse 268, 8057 Zurich, Switzerland.

Abstract

The immune mechanisms responsible for protection and pathogenesis in pneumoviral infection and cell-intrinsic pathways in airway epithelial cells are not well defined. Using a combination of in vivo and in vitro models we demonstrated that pharmacological activation of the hypoxic inducible factor (HIF) signalling axis, using the HIF-prolyl hydroxylase inhibitor Daprodustat limited viral replication through enhanced immune signalling. Transcriptomic analysis revealed HIF augmented activation of innate immune response genes, including interferon-stimulated gene 15 (Isg15), in the lungs and spleen of mice infected with the natural mouse pathogen, pneumonia virus of mice (PVM). In human respiratory syncytial virus (hRSV) infected airway epithelial cells, Daprodustat inhibited viral replication and enhanced ISG15expression in a HIF-dependent manner. Importantly, inhibition of type I interferon signalling or the RIG-I sensing pathway abrogated the antiviral activity of HIF, suggesting these pathways act in concert to limit viral replication. Moreover, Daprodustat treatment increased interferon signalling in response to RSV RNA, suggesting that HIF inhibits pneumovirus replication through enhancing viral RNA sensing, uncovering an innovative host-directed therapeutic approach. This study highlights the intricate interplay between cellular oxygen sensing and antiviral immunity and offers valuable insights into pneumovirus-host interactions and potential therapeutic interventions.

Subsets of Regulatory T Cells Are CD1a-Reactive and Dysfunctional in Psoriasis

Yi-Ling Chen

Main Talk

Lea Nussbaum[1], Rosana Ottakandathil Babu[1], Emily Zhi Qing Ng[2], Jessica Soo Weei Ng[1], Rachel Etherington[1], Karmella Naidoo[1,2], Janina Nahler[1], Fei Gao[1,2], Prathiba Kurupati[1], Tao Dong[1,2], Hashem Koohy[1], Graham S. Ogg[1,2], Yi-Ling Chen[1,2]

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2. *Chinese Academy of Medical Sciences Oxford Institute, Nuffield Department of Medicine, University of Oxford, UK.*

Abstract

Regulatory T cells (Tregs) contribute to skin homeostasis, but the antigenic targets remain unclear. The infiltration of Tregs is coincident with CD1a-expressing cells during skin inflammation, and whilst CD1a is known to present lipid antigens to effector T cells, the extent to which CD1a presents lipid antigens to Tregs has not been investigated. Here, we show CD1a reactivity in subsets of human circulating and cutaneous $CD4^+$ Tregs, displaying ab T cell receptors (TCRs), memory phenotypes and suppressive functions, including the ability to secrete interleukin-10 (IL-10) in response to the permissive lipid antigen lysophosphatidylcholine, known to be enriched in skin inflammation. Next, single-cell CITE-seq analyses of CD1a-reactive IL-10–producing $CD4^+$ Tregs from psoriatics showed maintenance of some canonical characteristics including LAG-3^+CD49b^+ expression, but with altered pro-inflammatory signatures including up-regulated type 1 and 17 effector function. In addition, clonally expanded IL-10–producing Tregs retained their suppressive phenotype in a CD1a- and TCR-dependent manner. Together, these findings show that subsets of Tregs are directed to self-lipid antigens and CD1a, but show an altered phenotype equipped with pro-inflammatory potential in the setting of psoriasis.

Induced-Proximity Strategies to Modulate Receptor Signaling in Inflammation and Cancer

Ricardo Fernandes

Main Talk

Victoria Junghans, Christina Heroven, Hugo Yan, Caitlin O'Brian-Ball, Khuluud Hussein, Raul Cioaca, Mai Vuong, Jeni Hsing and Ricardo A. Fernandes

Affiliations

1. *Chinese Academy of Medical Sciences Oxford Institute, Nuffield Department of Medicine, University of Oxford, UK.*

Abstract

Precise control of cell surface receptor signalling remains a central challenge in immunology and oncology. We have developed a suite of proximity-based approaches to modulate immune and oncogenic receptors by hijacking endogenous enzymatic machinery. Our original platform, Receptor Inhibition by Phosphatase Recruitment (RIPR), employs bispecific molecules to bring the CD45 phosphatase into close proximity with immune "checkpoint" receptors such as PD-1, CTLA-4, TIGIT, and LAIR-1, resulting in potent attenuation of signalling via targeted receptor dephosphorylation. This strategy circumvents the limitations of conventional checkpoint blockade by silencing receptor activity intracellularly at the membrane. Moreover, this strategy can be combined with classic receptor blockade. Recently developed RIPR molecules targeting CTLA-4 were found to potentiate T cell function beyond that achieved by standard checkpoint blockade approaches.

Building on the original RIPR concept targeting immune receptors, we have expanded our toolkit to target receptor tyrosine kinases (RTKs), including FLT3 and cKit. Through systematically mapping receptor-protein tyrosine phosphatase (RPTP) activity profile, we first established a connectivity map for RPTP's ability to target a set of 15 RTKs associated with cancer progression. Next, we demonstrated that the recruitment of CD45 to FLT3 can suppress oncogenic signalling and function in synergy with standard tyrosine kinase inhibitors to impact cell proliferation.

Conversely, to enhance signalling, we have developed kinase-recruiting bispecifics that act as soluble agonists for inhibitory receptors such as PD-1, BTLA, and CD200R. These molecules engage intracellular kinase-associated co-receptors and potentiate signalling without relying on Fc receptor engagement or cell-depleting mechanisms. In initial proof-of-principle experiments, we demonstrate that this new strategy can target CD4+, CD8+ or CD48+ T cell populations and dampen activation by triggering PD-1 or BTLA inhibitory signals. This Fc-independent design preserves the endogenous T cell repertoire while enabling immunosuppression of specific cell subpopulations, offering a tunable platform for treating inflammatory disorders.

Together, these induced-proximity strategies reveal new insights into receptor signal integration and provide a modular framework for therapeutic intervention across immune and cancer biology.

Computational Multistate Modeling and Immunological Synapse Analyses Reveal Bispecific T Cell Engager Quality Hierarchy in Treating Cancers

Tanmay Mitra
Dustin Group

Main Talk

Alexander Leithner#, Oskar Staufer#, Tanmay Mitra, Falk Liberta*, Salvatore Valvo, Mikhail Kutuzov, Hannah Dada, Jacob Spaeth, Sally Zhou, Felix Schiele, Sophia Reindl, Herbert Nar, Stefan Hoerer, Maureen Crames, Stephen Comeau, David Young, Sarah Low, Edward Jenkins, Simon J. Davis, David Klenerman, Andrew Nixon, Noah Pefaur, David Wyatt, Omer Dushek, Srinath Kasturirangan, Michael L Dustin*

Affiliations

1. *Chinese Academy of Medical Sciences Oxford Institute, Nuffield Department of Medicine, University of Oxford, UK.*

Abstract

Bispecific T-cell engagers (TcEs) link the T-cell receptor to tumour-associated antigens on cancer cells, forming a tumoricidal immunological synapse (IS). TcEs direct T cells to kill cancer cells by forming a cytotoxic IS. Structurally modular, they are engineered to simultaneously bind specific molecules on T cells and cancer cells. We engineered a panel of immunoglobulin-based TcEs linking CD3ε to Her2 covering a distance (~13 nm vs ~18 nm) and flexibility (low and high) matrix as determined by small angle X-ray scattering and membrane interface analysis. TcEs were analysed for killing potency, cytokine production, activation marker expression, adhesion capacity, and microscopy-based analysis of IS formation and signalling. To gain insight into TcE quality, we investigated four TcE formats (Formats A-D) that link CD3ε to a membrane proximal site in Her2. TcEs were constructed with (A) two N-terminal single-chain variable fragments (scFv) linked to the crystallizable fragment (Fc), (B) an N-terminal scFv and an N-terminal single-chain antigen-binding fragment (scFab) linked to Fc, (C) N-terminal scFabs linked to Fc, or (D) an N-terminal scFab linking to an Fc also bearing a C-terminal scFv. We measured the average span between paratopes and overall flexibility using small angle X-ray scattering (SAXS) and multistate modeling. Formats A and B spanned 11.4-12.6 nm, with B being more flexible than A. Formats C and D spanned 18.0-18.9 nm, with D being more flexible than C. All TcE induced cytotoxicity, with potency following the trend A>B=C>D. All TcEs facilitated equivalent T-cell-tumour cell adhesion. Formats A-C ISs formed rapidly and excluded CD45RABC, whereas Format D ISs formed slowly and included CD45RABC. We performed extensive molecular dynamics-based analysis on the multistate model structures to identify key differences in their structure-function relationship and characterized their intramolecular, translational and rotational flexibility, Shannon entropy and tilt properties. TcEs, both in isolation and complexed with antigens, exhibited intramolecular flexibility in the order A<B<C<D. For TcE-antigen complexes, translational and rotational flexibility followed the order B<A<C<D. Format A showed reduced flexibility when complexed with antigens, indicating conformational stabilization. Shannon entropy, representing effective disorder, ranked as A<B<C<D for TcEs embedded within antigens and A<C<B<D for whole TcE-antigen complexes. Our results suggest that a higher flexibility induced a penalty to TcE potency, which was helpful to link IS parameters to cytotoxicity. In summary, TcE quality hierarchy governs cytotoxic potency through adhesion, large ectodomain exclusion and recruitment of co-stimulation. Our research provides key insights into the performance of bispecific antibodies in treating cancers through computational and experimental pipelines.

Unveiling the Complete Spectrum of SARS-CoV-2 Fusion Stages by In Situ Cryo-ET

Caner Akil
Zhang Group

Main Talk

Caner Akıl[1,2], Jialu Xu[2], Juan Shen[2], Peijun Zhang[1,2,3]

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3. *Diamond Light Source, Harwell Science and Innovation Campus, Didcot, OX11 0DE, UK*

Abstract

SARS-CoV-2 entry into host cells is mediated by the spike protein, which drives membrane fusion. While cryo-EM has revealed stable prefusion and postfusion conformations of the spike, the transient intermediate states during the fusion process have remained poorly understood.

Here, we designed a near-native viral fusion system that recapitulates SARS-CoV-2 entry and used cryo-electron tomography (cryo-ET) to capture fusion intermediates leading to complete fusion. The spike protein undergoes extensive structural rearrangements, progressing through extended, partially folded, and fully folded intermediates prior to fusion-pore formation, a process that is dependent on protease cleavage and inhibited by the WS6 S2 antibody.

Upon interaction with ACE2 receptor dimer, spikes cluster at membrane interfaces and following S2' cleavage concurrently transition to postfusion conformations encircling the hemifusion and pre-fusion pores in a distinct conical arrangement.

Subtomogram averaging revealed that the WS6 S2 antibody binds to the spike's stem-helix, crosslinks and clusters prefusion spikes and inhibits refolding of fusion intermediates. These findings elucidate the complete process of spike-mediated fusion and SARS-CoV-2 entry, highlighting the neutralizing mechanism of S2-targeting antibodies.

Second-Generation Lymphoid Organoids for Mechanistic Studies of Human Immune Regulation

Pablo Céspedes Donoso

Main Talk

Delaney Dominey-Foy[1], Kexin Yu[1], Irene Kramer[1], Elke Kurz[2], Salvatore Valvo[2], Eve Warner[3], Evie Kite[3], Christine Jesus[3], David Maldonado-Perez[3], Michael L. Dustin[2], Jack Tan[4], Pablo F. Céspedes[1,]

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3. *The Oxford Radcliffe Biobank (ORB) & Oxford Centre for Histopathology Research (OCHRe), Nuffield Department of Surgical Sciences, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom.*
4. *MRC Weatherall Institute of Molecular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom.*

Abstract

Our overall goal is to establish human lymphoid organoids as essential toolkits for the reduction and replacement of animal models in immunology research. Lymphoid organoids enable the reorganisation of cell suspensions into follicle-like structures supporting germinal-centre (GC) reactions and T-cell activation, showing promise as methods to pivot the discovery of novel immune mechanisms regulating human adaptive immunity. However, their broader adoption is rather limited and a body of evidence supporting their application in various immunological and non-immunological settings is lacking. Here, we introduce our efforts to develop an antigen-agnostic, but antigen-dependent, second generation lymphoid organoid method supporting the mechanistic interrogation of enzymes and receptor-ligand interactions essential for T-cell communication. We further introduce our discovery framework and discuss the early adoption of this method to study immune response to vaccines and pathogens, and our plans to develop the technology further.

Understanding Immunology and Disease Pathogenesis with an Integrated Bioinformatics Platform

Elie Antoun
Dong/Knight Group

Main Talk

Elie Antoun[1], Maria Veretennikova[1], Yanchun Peng[1,2], Tao Dong[1,2], Julian Knight[1,3]

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Abstract

The complexity of the immune system, coupled with the rapid advancements of high-throughput sequencing and single-cell technologies, has created a need for specialized tools to manage, analyse, and interpret next generation sequencing data. Within the COI, we have a bioinformatics platform specifically designed to support all aspects of both immunology research and wider data analysis, enabling comprehensive analysis of immune repertoires, transcriptomes, epigenomes, and multi-'omic' datasets, in immunology and disease.

This platform offers end-to-end workflows tailored to key immunological applications and questions, such as T and B cell receptor (TCR/BCR) repertoire profiling, cytokine signalling analysis, immune cell phenotyping, and investigation of the antigen-specific response. We are able to provide pipelines for data pre-processing, advanced clustering and basic annotation, for both single-cell and bulk datasets, as well as increased capacity for spatial analysis. Data can be further integrated with key immunological databases (e.g., VDJdb, ImmPort, and IEDB) for deeper exploration.

The platform has investigated datasets originating from infectious disease and cancer, demonstrating how we are able to provide support for deep immune profiling, biomarker discovery, and mechanistic insight. We aim to highlight the overall bioinformatic capabilities, analytical and study design, and its role in accelerating translational immunology research through data-driven insights.

From COI to Start-up: Our Journey from Discovery to Company

Ricardo Fernandes

Main Talk

Ricardo A. Fernandes

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Abstract

We will share the story of how a fundamental discovery in receptor signalling made in an academic lab at COI evolved into a start-up. From the outset, the project was supported by COI and driven by a passionate team of students and postdocs. With support from COI, NDM, and Oxford University Innovation (OUI), we navigated the IP landscape, engaged with investors, and gained first-hand experience of how academic-led innovation can be translated into an early-phase biotech.

FLASH TALKS

Session 1

Chair: Christina Heroven

Session 2

Chair: Nikolaos Kanellakis

Session 3

Chair: Yanchun Peng

Mapping Specificity and Cross-Reactivity of Wild-Type and Engineered T Cell Receptors

Kristen Koopmans
Fernandes Group

Flash Talk

Kristen E. Koopmans, Adam Bates, Dan Hudson, Elie Antoun, Yanchun Peng, Tao Dong, Ricardo Fernandes

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Abstract

T cells identify cancer and infected cells via their T cell receptor (TCR) which recognises peptides presented by the major histocompatibility complex (pMHC). Deciphering the principles of TCR-pMHC interactions and origins of cross-reactivity remains a major challenge for developing efficient TCR-based immunotherapies. Here, we developed a workflow to characterise the binding landscape and cross-reactivity of tumour-reactive TCRs through affinity-based selections of pMHC yeast display libraries, coupled with computational, functional and structural analysis.

For the affinity-enhanced TCR, Tebentafusp, peptide enrichment analysis revealed conserved motifs strikingly similar to the gp100 peptide. Despite this, Tebentafusp displayed reactivity to off-target WT peptides with substitutions tolerated at P6. Notably, T cell activation differed based on whether TCR recognition was via the cell-bound or soluble form. In contrast, TCR 350, a WT orphan TCR isolated from a non-small cell lung cancer biopsy, recognised two distinct peptide motifs, highlighting the role of cross-reactivity in tumour antigen recognition. Using novel in silico workflows, we predicted and confirmed binding to several wild-type candidate peptides. Structural predictions support the motif pattern where the TCR exclusively binds the C-terminus, permitting N-terminus promiscuity.

By deconvoluting the complexities of TCR-pMHC interactions, we can use this to understand the molecular fingerprints associated with cross-reactivity to de-risk candidate therapeutic TCRs, de-orphanise disease-relevant TCRs and identify novel antigen targets.

Linking Function to Location: Adapting a Spatial TCR Sequencing Approach to Study Antigen-Specific T Cells in Tissue

Zinan Yin
Dong Group

Flash Talk

Zinan Yin[1], Elie Antoun[1], George Adigbli[1,2], Guihai Liu[1],Yanchun Peng[1], Fadi Issa[1,2], Tao Dong[1]

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Abstract

Understanding the spatial organisation of antigen-specific T cells in tissue is essential for dissecting local immune responses in health and disease. To address this, we are establishing a spatially resolved T cell receptor sequencing (spTCR-seq) platform that combines spatial transcriptomics with targeted TCR enrichment and long-read sequencing to map TCR clonotypes within tissue architecture. In parallel, antigen-specific T cells are identified using functional T cell assays, including T cell culture, activation-induced marker (AIM) assays, and peptide–MHC tetramer staining, followed by phenotypic and transcriptomic profiling. We have optimised the spTCR-seq workflow for high-quality TCR capture and are integrating this with functionally annotated TCR data to enable future spatial localisation of antigen-specific clones. This methodological framework provides a foundation for in situ analysis of T cell clonality, phenotype, and spatial context, with broad applications in infection, cancer, and other immune-related diseases.

Spatial Analysis of the Chronic Hepatitis B and D Liver Reveals New Aspects of Viral Pathogenesis and Cancer

Nadina Wand

McKeating Group

Maria Veretennikova

Dong Group

Flash Talk

Nadina Wand[1], James Harris[1], James Lok[2], Maria Veretennikova[3], Ian Fiddes[4], Medhi Boutasbih[1], Joanna Hester[5], Hareem Maune[4], Ivana Carey[2], Fadi Issa[5], Kosh Agarwal[2], Yoh Zen[2] & Jane A McKeating[1,3]

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Abstract

Hepatitis B and D viruses are a major health problem with >20 million infected people worldwide at risk of developing cirrhosis and liver cancer. HDV coinfection associates with an accelerated course of liver disease, however, the molecular pathways leading to cirrhosis and hepatocellular carcinoma (HCC) are not well defined. Currently available treatments do not cure infection, highlighting an urgent need for new therapies. Our limited knowledge of the mechanism(s) underlying hepatitis B and D pathogenesis and lack of in vitro or small animal models that develop disease are major roadblocks to progress.

Spatial transcriptomics provides unprecedented insights into patterns of gene expression, making it a valuable tool for studying tissue architecture and disease aetiology. Recent advances in tissue transcriptomics allows single-cell resolution and integrating probes to quantify both viral and host gene expression offers unique insights into the behaviour of individual infected hepatocytes in the context of native tissue.

Our recent studies of HBV mono-infected and HDV-HBV co-infected tissue show a significant upregulation of interferon, inflammatory, epithelial-mesenchymal transition and pro-oncogenic signalling pathways in hepatitis B/D co-infected cells and HBV-integrant bearing hepatocytes. Extending our transcriptomic analysis from virus infected cells to adjacent hepatocytes and non-parenchymal cells allowed the identification of viral niches that were enriched for Natural Killer, fibroblasts and T cells and integrating transcriptomic data with tissue pathology uncovers an overlap with areas of inflammatory damage.

These findings highlight the power of spatial molecular virology combined with pathology to uncover the cellular and molecular basis of viral-associated liver disease.

Immunosuppression Drives a Skewed Chemokine Landscape Associated With Altered T Cell Infiltration in Post-Transplant Cutaneous Squamous Cell Carcinoma

Girishkumar Kumaran
Bottomley Group

Flash Talk

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Abstract

Organ transplantation requires recipients to take long-term pharmacological therapy to suppress immune responses against the transplant. Immunosuppression non-specifically impairs immunosurveillance and promotes premalignant change, leading to elevated incidence and mortality of post-transplant cancer. Cutaneous squamous cell carcinoma (CSCC) is the most common malignancy in this cohort. Whilst reduced effector T cell infiltration is seen in post-transplant CSCC, the mechanisms driving altered T cell dynamics are unknown.

Utilizing multi-modal spatial profiling of CSCC from kidney transplant recipients (KTR) and non-immunosuppressed controls (NIC), we identify enhanced fibrovascular niche development with a globally impaired immune response and enhanced tumor aggression in KTR. Loss of effector T cell infiltration is associated with a skewed chemokine milieu, favouring Th2/ regulatory T cell recruitment in a CCR8-dependent manner. Alterations in signaling pathways including MAPK and NF-κB was seen, which may drive this effect.

This study demonstrates that pharmacological immunosuppression drives chemokine dysregulation, leading to impaired recruitment and function of effector T cells in post-transplant CSCC. It reveals hitherto unknown mechanisms by which T cell tumoral immunity is depressed after transplant, potentially providing a novel approach to prevent and treat post-transplant malignancy.

Comprehensive Characterization of Tumor-Specific CD8 T-Cells in HR+ Breast Cancer Patients Reveal an Impaired Antitumoral Response in Patients With Lymph Node Metastasis

Mariana Pereira Pinho
Dong Group

Flash Talk

Mariana Pereira Pinho[1,2], Elie Antoun[2], Balraj Sandhar[1,2], Ting Shu[2], Fei Gao[1,2], Xiaobao Yang[2], Lucia Cerundolo[3], David Maldonado-Perez[3], Renuka Teague[3], Adam Bates[1,2], Megat H. B. A. Hamid[2], Eve Warner[3], Lucinda Winter[4], Nasullah Khalid Alham[5,6], Clare Verrill[3,6], Simon Lord[7], Timothy Rostron[1], Sally-Ann Clark[1], Craig Waugh[1], Paul Sopp[1], Chris Conlon[2], Ricardo A. Fernandes[2], Adrian L. Harris[7], Yanchun Peng[1,2], Asha Adwani[8], Tao Dong[1,2]

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Abstract

Background: Most breast cancers express hormone receptors, but the antitumor immune response of these hormone receptor-positive (HR+) breast cancer remains poorly characterized.

Method: Dendritic cells loaded with tumor lysate were used to identify tumor-reactive CD8 T cells in HR+ breast cancer patients. These cells were sorted and their specificity were confirmed by culture with tumor cell lines and tumor-associated antigens. The antitumor TCR repertoire was analyzed by sequencing the TCR of the tumor-specific CD8 T cells.

Results: Tumor-reactive CD8 T cells were detected in most HR+ breast cancer patients, especially those with early-stage tumors. When present, the circulating antitumor CD8 response contained cytotoxic T cells with diverse specificity and TCR repertoire. Additionally, patients with circulating cancer-specific T cells had significantly more CD8 tumor-infiltrating lymphocytes (TILs). Moreover, tumor-specific TCR sequences were found in the tumor, but at a significantly lower proportion in patients with lymph node involvement.

Conclusions: Our data suggest that HR^+ breast cancer patients with lymph node metastasis lack tumor-specific CD8 T cells with capacity to infiltrate the tumor at significant levels. However, early-stage patients have a diverse antitumor CD8 response that could be harnessed to develop immunotherapeutic approaches for late-stage HR^+ patients.

CD1a Contributes to Early Bacterial and Stress Sensing in the Skin

Karmella Naidoo
Ogg Group

Flash Talk

Karmella Naidoo[1,2], Clare Hardman[1], Adrian Kobiela [1], Laura Ciacchi[1], Esther Bridges[1], Rosana Ottakandathil Babu[1], Jessica Soo Weei Ng[1], Yi-Ling Chen[1,2], Uzi Gileadi[1], Alison Simmons[1], and Graham Ogg[1,2]

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Abstract

Background: During atopic dermatitis (AD) flares the skin has an altered microenvironment which include skin barrier dysfunction, changes in skin pH, increased immune dysregulation and microbial dysbiosis all of which can directly contribute to cutaneous inflammation. Cluster of differentiation 1a (CD1a) is an HLA class-I-like molecule that is highly expressed by Langerhans cells (LCs), ideally positioned within the epidermal compartment to detect breaches in the cutaneous barrier, but the role in microbial and stress sensing has not been extensively investigated. Our study aims to determine the role of CD1a in sensing stress changes, using a murine model that closely resembles AD-like phenotype observed in patients.

Methods: MC903, a vitamin D analogue, was topically applied to the skin of humanised CD1a transgenic mice (CD1atg) and controls, in the presence or absence of topical antibiotics. In addition, we assessed the role of pruritus by utilizing veterinary fitted collars, preventing specific groups from scratching during the early stages of the MC903 model and evaluated the role of a key itch mediator, TSLP. Skin thickness, scratching behaviour, immune cell infiltration and tissue cytokine and chemokine levels were assessed.

Results: Preliminary data revealed a profound skin alarmin signature, increased skin inflammation, itching, compromised barrier integrity and microbial and immune dysregulation, in the setting of CD1a {e.g. MC903 induced ear thickness in CD1atg ≈ 450um compared to ≈ 330um in WT respectively ($p<0.001$)}. Antibiotic application in the MC903 model, led to a significant reduction in disease parameters, inflammatory cells and cytokines, that was particularly associated with the presence of CD1a.

Conclusion: The amplified dermatitis-like phenotype induced by MC903 in CD1atg suggests a role for CD1a extending far earlier in the AD inflammatory pathway than expected. Furthermore, our findings reveal potential insights into CD1a biology and its involvement in early bacterial and stress sensing in the skin.

Loop Extrusion by Cohesin Plays a Key Role in Enhancer Activated Gene Expression During Differentiation

Felice Hoching Tsang
Higgs Group

Flash Talk

Felice H. Tsang[*,1,2], Rosa J. Stolper*[*,2], Emily Georgiades[2], Lars L.P. Hansen[2], Damien J. Downes[2], Jim Hughes[2], Robert Beagrie[2], Benjamin Davies[3], Mira T. Kassouf[2], Douglas R. Higgs[1,2]*

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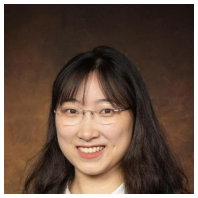
**These authors contributed equally: Rosa Stolper, Felice Tsang*

Abstract

Cis-regulatory elements such as promoters and enhancers are the fundamental DNA sequences controlling transcription and are thought to come into proximity to drive gene expression. This proximity may be explained by a variety of mechanisms; most recently via cohesin-mediated chromatin loop extrusion. In the loop extrusion model, the translocation of cohesin along the chromatin may bring enhancers and promoters, which are linearly separated, into proximity, thereby initiating transcriptional activation. However, despite the compelling nature of this hypothesis, acute depletion of cohesin in mouse embryonic stem cells (mESCs) does not result in widespread changes in gene expression. Given the non-differentiating nature of mESCs, we have set out to further explore the role of cohesin and loop extrusion in gene expression regulation during differentiation.

To examine the role of cohesin in mammalian gene regulation, we utilized the well-characterized mouse alpha-globin locus as a model. We have demonstrated that acute depletion of the cohesin core subunit RAD21 leads to a significantly downregulation of alpha-globin expression at early stages of erythroid differentiation, but not at later stages. Orthogonally, we found that blocking cohesin extrusion by introducing ectopic single or multiple CTCF sites between the alpha-globin enhancers and promoters resulted in diminished enhancer-promoter interaction and subsequent reduction in the alpha-globin gene expression. Notably, when these CTCF sites were introduced in two orientations, we observed a stronger reduction of alpha-globin expression when the CTCF sites were oriented towards the enhancers. This observation suggests that within this activated domain, cohesin predominantly but not exclusively translocates from the enhancers to the promoters. Taken together, our findings suggest that cohesin-mediated loop extrusion does play a pivotal role in establishing enhancer-promoter proximity and consequent expression of inducible genes during differentiation.

Multi-Omic Approach Reveals Neutrophil Heterogeneity in Pleural Infection



Yinzhou Feng
Kanellakis Group

Flash Talk

Yinzhou Feng[1], Kiki Cano-Gamez[2], Andrew Brown[2], Julia Y. Chu[1], Alguili Elsheikh[3], Nikita Manoharan[1], Tao Dong[1], Najib M. Rahman[3], Julian C. Knight[2], and Nikolaos I. Kanellakis[1]

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Abstract

Background: Pleural infection is a severe and complex disease with increasing incidence worldwide. The profile of neutrophil subsets and neutrophil extracellular traps (NETs) in pleural infection remains unclear.

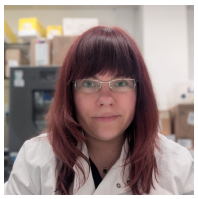
Aim: This study aims to investigate the neutrophil repertoire and its association with clinical outcomes.

Methods: Single-cell RNA sequencing (scRNA-seq) and mass spectrometry were performed on paired whole blood and pleural fluid samples collected from pleural infection patients (n=4).

Results: Unsupervised clustering of scRNA-seq data (45,143 neutrophils) identified eight neutrophil subsets. There was a significant heterogeneity between blood and pleural fluid neutrophils. Immature neutrophils (IL1R2+ and PADI4+) were exclusively detected in the blood, while pleural fluid neutrophils were highly activated with a higher proportion of four activated clusters. Other clusters seen in both compartments included mature neutrophils (MPO+ and S100A8/9+), interferon-responsive neutrophils (IFI6+), and adhesive neutrophils (CD18+). Mass spectrometry analysis revealed higher expression of neutrophil elastase and S100A8/9 in pleural fluid, while plasminogen was elevated in the blood. KEGG pathway analysis highlighted the upregulation of the advanced glycation end product (AGE)-receptor for AGE (RAGE) signaling pathway in pleural fluid, marked by Cell Division Cycle 42(CDC42) and Fibronectin 1(FN1), suggesting enhanced neutrophils adhesion and migration in pleural fluid.

Conclusion: This study identified eight distinct neutrophil subsets with different maturation and activation states and highlights differences in the cellular environment of blood and pleural fluid during pleural infection.

Potent and Broadly Neutralising Antibodies Against Sarbecoviruses Elicited by SARS-CoV-2 Infection



Aiste Dijokaite-Guraliuc
Screaton Group

Flash Talk

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Abstract

The emergence of various SARS-CoV-2 variants presents challenges for antibody therapeutics, emphasising the need for more potent and broadly neutralising antibodies. We employed B cell screening approach and successfully generated 5 antibodies from vaccinees suffering various breakthrough infections. Two of these antibodies, JN.1-4 and JN.1-5, exhibited robust cross-neutralisation against a spectrum of SARS-CoV-2 variants, including the latest KP.3, XEC and LP.8.1.1, with consistent IC50 values ranging around 100μg/mL. They also displayed broad neutralisation activity against SARS-CoV and related sarbecoviruses such as GX-P4L, Khosta-2, Banal-236 and others. Structural analysis revealed that these antibodies target lower-right flank and are tilting towards the back of the RBD. Residues involved in binding are highly conserved across some bat coronaviruses and SARS-1. These findings suggest that antibodies with cross-neutralization activities can be identified from individuals with ancestral virus exposure and/or vaccination.

Neutrophil Elastase and NETs Contribute to Disease Exacerbation in Pleural Infection

Julia Y. Chu
Kanellakis Group

Flash Talk

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Abstract

Background: Approximately 30% of pleural infection patients fail the first line treatment of antimicrobial therapy and require intrapleural enzyme therapy. Plasminogen Activator Inhibitor 1 and Soluble Urokinase Plasminogen Activator Receptor have been investigated as fibrinolytic deficiency biomarkers. Neutrophil elastase (NE) was recently suggested to inhibit fibrinolysis by degrading plasminogen and thereby increasing the likelihood of septation.

Aim: To investigate the effect of neutrophil elastase on fibrinolysis and clinical outcome using clinical samples from pleural infection patients across several independent studies.

Results: We found a negative correlation between the protein level of pleural neutrophil elastase and plasminogen (r= -0.5120, p=0.002**) or D-dimers (r= -0.1419, p=0.04*). Inhibiting NE reduced plasminogen degradation, confirming the involvement of NE in the fibrinolytic deficiency (p=0.0028**). Pleural infection patients with significantly higher levels of NE-neutrophil extracellular traps (NETs) in their pleural fluid are more prone to develop septation (p=0.0135*) and showed poorer survival (p=0.04*). Moreover, intrapleural enzyme therapy reduces the level of neutrophil-derived proteins including NE, myeloperoxidase and S100A8/A9, as well as NETs complex in pleural fluid.

Conclusion: In conclusion, our data demonstrates the contribution of NE and NETs in the intrapleural fibrinolytic deficiency. Both pose as potential important targets for disease management.

Identifying Tumour-Cell-Intrinsic Genes That Mediate Resistance to T Cell Recognition and Cytotoxicity

Nicole Fletcher
Dong Group

Flash Talk

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Abstract

CD8$^+$ T cells are key effectors of the antitumour immunity, and immunotherapy has revolutionised cancer treatment by enhancing the ability of CD8$^+$ T cells to recognise and eliminate tumour cells. However, most patients do not respond. This resistance can stem from tumour-cell-extrinsic factors within the tumour microenvironment (TME), as well as tumour-cell-intrinsic factors such as gene expression patterns that limit CD8$^+$ T cell infiltration,activation, or function. While pooled CRISPR-Cas9 screens have been successful in identifying some of these tumour-cell-intrinsic resistance mechanisms, many remain poorly understood due to limitations in current screening strategies.

In this study, we used the genome-wide Humagne CRISPR-Cas12a knockout library and a patient-derived tumour-specific CD8$^+$ T cell clone to identify genes that mediate tumour-cell-intrinsic resistance to CD8$^+$ T cell activation and effector functions, enhancing the relevance to the TME and improving the identification of hits. Among the identified genes, *ITGBL1* emerged as a key modulator of CD8$^+$ T cell cytotoxicity. Our analysis of a publicly available RNA-seq dataset from melanoma patients revelated that high ITGBL1 expression is enriched in non-responders to immunotherapy. We further demonstrated that ITGBL1 suppresses CD8$^+$ T cell activation and cytokine production with *in vitro* functional studies. These findings establish ITGBL1 as a novel regulator of CD8$^+$ T cell-mediated antitumour immunity, with potential as both a therapeutic target and biomarker to improve immunotherapy outcomes. Investigating ITGBL1's downstream signalling pathways may reveal insights into the molecular mechanisms of suppression.

Tumour Cells in Transit: Single-Cell Analysis of Lymphatic CTCs in Stage III Melanoma

George Adigbli
Issa Group

Flash Talk

George Adigbli, Elie Antoun, Guihai Liu, Yuxi Wu, Zinan Yin, Yuxin Zeng, Oliver Cassell, Fadi Issa, Ji-Li Chen, Yanchun Peng, Tao Dong

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Abstract

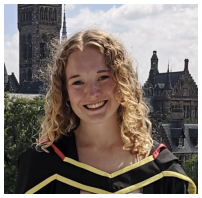
Introduction: Liquid biopsy is a transformative diagnostic tool for the early detection and monitoring of cancer. In melanoma however, blood-based liquid biopsies have demonstrated limited utility in early-stage disease. This likely reflects melanomas propensity to spread initially through lymphatics rather than the blood, resulting in minimal tumour-derived material entering the bloodstream during early dissemination. We hypothesise that tumour-draining lymph may offer a more enriched substrate for detecting early metastasis. To begin evaluating this approach, we analysed lymph from patients with radiologically confirmed lymph node metastases undergoing surgical lymphadenectomy.

Methods: We prospectively collected lymph and corresponding lymph node tissue from three Stage III melanoma patients undergoing lymphadenectomy. Using single-cell RNA sequencing, we profiled cells from both sample types to identify Lymph-derived circulating tumour cells (L-CTCs) and compared their transcriptomic signatures to metastatic cells in the affected lymph node basins.

Results: L-CTCs were identifiable in the lymph of all three patients, marked by expression of established melanoma-associated genes including MLANA and PMEL. Clustering of both L-CTCs and lymph node metastatic cells aligned with previously characterised melanoma populations with metastatic potential. Notably, compared to established lymph node metastases, L-CTCs exhibited differential expression of several prognostic genes, suggesting they may reflect a molecular state associated with early dissemination.

Conclusion: These preliminary findings demonstrate the feasibility of collecting lymph during routine lymph node surgery to detect melanoma CTCs. The observed transcriptional differences between L-CTCs and nodal metastases suggest that lymph may contain transiting tumour cells with molecular signatures relevant to metastatic progression. This pilot offers early support for further investigation into lymph liquid biopsy as a potential tool for understanding early metastatic behaviour in melanoma.

Investigating Functional Effects of Integrin Expression on SARS-CoV-2 Virus-Specific CD8+ T Cells and Their Potential Impact on Pathology



Maya Pidoux
Dong Group

Flash Talk

Maya Pidoux[1,2], Kexin Yu[1], Elie Antoun[1], Fei Gao[1], Zinan Yin[1], Pablo Cespedes Donoso[1], Yanchun Peng[1,2], Tao Dong[1,2]

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2. *MRC TIDU, WIMM, RDM, University of Oxford*

Abstract

Proteomics analysis of HLA-A*01:01 restricted SARS-CoV-2 ORF3a$_{207\text{-}215}$ specific CD8$^+$ T cell clones revealed different integrin expression profiles between clones bearing the same T cell receptor. Integrins, which function as α/β heterodimers, are cell adhesion molecules with known roles in immune cell trafficking but their functional effects on T cells and their interplay with TCR signalling remains less well understood. This study further explores the effect that the integrins α4β7 and α4β1 have on CD8+ T cell function.

We utilised *in vitro* functional assays to determine the cytokine production, killing capacity and proliferative capacity of ORF3a$_{207\text{-}215}$ specific CD8$^+$ T clones. Whole-cell proteomics was performed to determine differences in protein expression between functionally distinct clones. Using blocking antibodies targeting α4β7 and α4β1 we investigated the functional effect of these integrins on T cells. We used supported lipid bilayers and total internal reflection fluorescence microscopy (TIRFM) to determine the localisation of these integrins in the immunological synapse.

We found that functionally distinct ORF3a$_{207\text{-}215}$ specific CD8$^+$ T clones that bear the same TCR show differences in their integrin expression profile. The functionally superior clones have higher expression of the integrins α4β7 and α4β1. Through stimulation with the integrin ligands MadCAM-1 and VCAM-1 we found that these integrins can increase cytokine production of CD8+ T cells. Pharmacological blockade of α4β7 and α4β1 in a coculture with VCAM-1+ antigen presenting cells reduces cytokine production from CD8+ T cells. We observed increased localisation of the integrins α4, β7 and β1 in the immunological synapse in the presence of their ligands.

Overall, our findings highlight a functional role of the integrins α4β7 and α4β1 in modulating CD8$^+$ T cell responses and suggest that these integrins may act as fine tuners of T cell activity.

Memory HBx-Specific T Cells Associate With Viral Control

Guihai Liu
Dong Group

Flash Talk

Guihai Liu, Yanchun Peng, Xuan Yao, Guifang Qiao, Qin Ling, Craig Waugh, Ushani Rajapaksa, Yonghong Zhang & Tao Dong**

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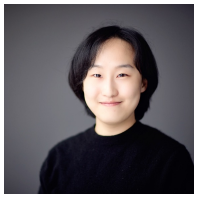
Abstract

Chronic hepatitis B virus (HBV) infection is a global public health problem that leads to substantial liver-related morbidity and mortality. HBV-specific T cell responses are critical in controlling HBV infection, but little is known about the role of HBV x protein (HBx)-specific T cells. Here, we investigated HBx-specific T cell responses in patients with chronic HBV infection (n=71) and functional cure (n=17) by *ex vivo* IFNγ ELISpot and evaluated the functional profile of those T cells including cytokine production, antigen sensitivity, cytotoxicity and anti-viral activity *in vitro*. We identified and isolated HBx-specific T cells targeting one $CD8^+$ (X_{146}) and three $CD4^+$ epitopes (X_{29}, X_{89} and X_{105}) from participants with HBx-specific T cell responses. To evaluate anti-viral efficacy, $HepG2^{hNTCP}$ cells were infected with HBV then cocultured with HBx-specific T cells for intracellular cytokine staining, killing assay and the suppression fo HBV replication. We found that X_{146}-specific $CD8^+$ T cells can produce effector cytokines and express CD107a when encountering HBV-infected $HepG2^{hNTCP}$ cells. Furthermore, they can efficiently kill HBV-infected cells and suppress HBV replication with dramatic reduction of HBsAg and HBeAg in the supernatant. HBx-specific T cells against the three $CD4^+$ epitopes displayed distinct antigen sensitivity, cytokine profile and cytotoxicity. X_{89}-specific cells showed the greatest cytotoxicity, while X_{105}-$CD4^+$ T cells did not exhibit any killing capacity. Interestingly, highly cytotoxic HBx-specific $CD4^+$ T cells have high functional avidity and degranulation (CD107a expression). X_{89}-specific $CD4^+$ T cells repressed HBV replication in $HepG2^{hNTCP}$ cells by both cytolytic and noncytolytic effector mechanisms. *Ex vivo* HBx-specific T cell responses were correlated with HBeAg clearance and lower HBsAg levels in patients with chronic HBV infection. This study demonstrates the potent role of HBx-specific T cells in controlling HBV infection and highlights their potential for future interventions.

SSX2 Reactive High Functional Avidity TCR for Tumour Adoptive Cell Therapy



Fei Gao
Dong Group

Flash Talk

Fei Gao, Yanchun Peng, Mariana Pereira Pinho, Nikolaos Kanellakis, Yi-Ling Chen, Uzi Gilead, Graham Ogg, Tao Dong

Affiliations

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Abstract

Cancer-testis antigens (CTAs) have been seen as ideal immunotherapy targets for effective tumour control due to their aberrant expression in human malignancies, yet with restricted expression in normal tissues. From the previous work, our lab reported the successful isolation and characterization of tumour reactive T cell clones with specificity for synovial sarcoma X breakpoint 2 (SSX2) and these T cell clones demonstrated potent anti-tumour T cell responses in the ex-vivo tumour suppression assays. In the present work, by using the non-viral orthotopic TCR replacement system, we systematically compared these two HLA*A0201 restricted SSX2 antigen reactive TCRs. Primary CD8 T cells redirected by these two TCRs demonstrated potent SSX241-49 peptide reactivity and tetramer specific binding, while distinct functional avidity was seen for these two TCRs. The high functional avidity TCR had higher tetramer binding potential and showed higher T cell responsiveness towards different patient derived SSX2 antigen positive tumour cell lines. In addition, this TCR was CD8 independent and could effectively redirect CD4 T cells responding to the MHC-I restricted SSX241-49 epitope, providing extra “helper” functions by releasing multiple cytokines or even direct tumour cell killing. Moreover, this TCR was also proved effective in redirecting unconventional T cells, such as cytolytic NKT or γδT cells as alternative T cell subsets for effective tumour control. In summary, this study demonstrated SSX2 targeting high functional avidity TCR as an attractive candidate for potential TCR based therapeutics for future tumour immunotherapy.

Investigating USP18 as a Target in Immuno-Oncology

Simeon Draganov
Pinto-Fernández Group

Flash Talk

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Abstract

The ubiquitin-specific protease 18 (USP18) is an interferon-stimulated gene (ISG) that acts as a negative regulator of the Type I interferon (IFN) response and is important for immunomodulation.[1,2] Recent studies indicate that USP18 plays important roles in regulation of the T cell functional response in the context of immuno-oncology.[3] Previous data from our lab with wild-type (WT) and USP18 knockout (KO) cancer cell lines indicate that there is an increased T cell killing response towards USP18 KO cancer cells in T cell killing co-culture assays, increased activation of T cells in the USP18 KO co-cultures, and increased MHC-I antigen presentation on USP18 KO cancer cells.[3] Furthermore, *in vivo* studies with WT and USP18 KO colorectal tumour engrafts in immunocompetent mice show a significantly lower (~90%) tumour growth rate for the USP18 KO tumour, indicating the relevance of USP18 in suppressing tumour eradication by the immune system.[4] Here, we investigate additional roles of USP18 in the T cell functional response. We uncovered a novel, previously undescribed role of USP18 in suppression of T cell migration (chemotaxis). Proteomics analysis and comparison of WT and USP18 KO cell culture media of a chronic myeloid leukaemia cell line revealed ~1000-fold higher levels of the chemokine CXCL10 in the cell culture media of USP18 KO cells, and subsequent chemotaxis assays revealed a strong T cell migration effect in the USP18 KO cell culture media arising as a result of CXCL10 secretion. Our data provides strong evidence that USP18 may be a vital target in immuno-oncology, and we anticipate that targeting USP18 through catalytic and/or protein-protein interaction inhibitors or by direct degradation through PROTACs/molecular glues may represent a novel therapeutic strategy in immuno-oncology.

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COI Professional Support Sevices Team	*PSS Team*
COI Scholarship Programmes	*PSS Team*
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Advanced Kidney Disease Drives Shifts in the Cutaneous Transcriptome, Associating With Altered T Cell Differentiation

Noushin Zibandeh
Bottomley Group

Poster

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Abstract

Introduction: Itching, or pruritus, of skin is a common and debilitating symptom experienced by patients with chronic kidney disease (CKD) and end-stage renal disease (ESRF). In addition, the incidence of skin infections and cancer is elevated in individuals with uraemia. This is thought to be due to impaired immune surveillance, extrapolating from alterations in circulating leucocyte populations (including accelerated immune ageing). Little research has taken place to evaluate this assertion. Novel unbiased sequencing approaches permit detailed analysis to evaluate alterations in pathways associated with uraemia.

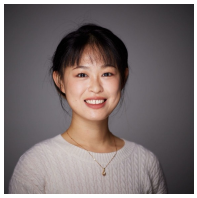
Objectives: To investigate the impact of uraemia on cutaneous immunity in non-diseased skin by comparing immune and non-immune cell populations in skin samples from patients with ESRF at the time of kidney transplantation to those from age-matched healthy controls.

Methods: In an ongoing prospective case-control study, paired blood and healthy abdominal skin were collected from age-matched Caucasian patients with (n=21, cases) or without (n=22, healthy controls) ESRF. Skin was processed for flow cytometry, immunohistochemistry and single-cell RNA data analysis.

Results: Skin-resident CD4 and CD8 T cell proportion and dermal density did not differ in cases compared to controls. Uraemia was not associated with enhanced immune ageing in blood or skin, though CD57 expression was significantly enriched in cutaneous CD4+ and CD8+ T cells ($p<0.001$) compared to peripheral blood. Circulating CD57 expression did not significantly correlate with skin expression. Single-cell gene expression analysis of skin cell populations revealed changes in the proportions of specific cell types, notably an increase in vascular cells and a decrease in a subset of keratinocytes, aligning with patterns typically seen during inflammation.

Conclusion: Our findings suggest that circulating immune age is not enhanced in patients with ESRF undergoing transplantation. Changes in circulating T cell phenotype associated with immune ageing correlate poorly with alterations in cutaneous T cells.

Aged Macrophages: Diminished Metabolic Flexibility but Not Pro-Inflammatory Bias as a Driver of Inflammageing in Humans



Haichen Hu
Maeyer Group

Poster

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Abstract

Ageing is characterized by a systemic, low-grade inflammation ("inflammageing") that underlies multiple chronic disease. Macrophages—professional phagocytes and key effectors of tissue homeostasis—undergo functional and metabolic decline with age, yet the mechanisms in humans remain unclear. Here, we combine functional assays with metabolic profiling to dissect age-related shifts in human macrophage efferocytosis.

Monocyte-derived macrophages (MDMs) from healthy young (20–35 y) and elderly (65–80 y) donors were challenged with LPS or apoptotic cells to assess inflammatory responses and efferocytosis. Contrary to prevailing beliefs, aged macrophages did not show significant age-related shifts toward a pro-inflammatory phenotype as inflammatory surface markers and cytokine release were equivalent across age groups. Yet, aged MDMs exhibited a significant reduction in both phagocytic and efferocytotic capacity. This suggests that cell-clearance failure, rather than chronic pro-inflammatory activation, drives macrophage-mediated inflammageing.

To explore underlying metabolic shifts, we measured MitoTracker and glucose transporter-1 (GLUT1) expression by flow cytometry. Young MDMs exhibited higher membrane potential and lower baseline GLUT1 than aged MDMs. Following efferocytosis, young macrophages rapidly increased GLUT1 within 1 h, whereas aged cells required longer to upregulate and sustain GLUT1 levels at 24 h. These data indicate that young macrophages rely on robust oxidative phosphorylation for efficient clearance, while aged macrophages compensate for mitochondrial decline by shifting toward glycolysis. Bulk RNA-seq of young versus aged MDMs further identified gene clusters enriched for OXPHOS and cell migration in young cells, corroborating the functional assays.

Together, our data redefine macrophage involvement in inflammageing: age-related defects in metabolic plasticity—diminished mitochondrial fitness and delayed glycolytic adaptation—impair apoptotic-cell clearance instead of directly boosting pro-inflammatory cytokine production. Future work will test metabolic interventions in human immune-challenge models to restore macrophage clearance functions and resolve inflammageing, opening avenues for therapies that target macrophage metabolism to preserve tissue health in the elderly.

Characterisation of Human IgAN Renal Biopsies by Spatial and Single Cellular Profiling Reveals Cell Type Specific Disease Signatures and Crosstalk

Jessica D. Kepple
Bull Group

Poster

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4. *Oxford Kidney Unit, Oxford University Hospitals Trust*

Abstract

Background: IgA nephropathy (IgAN) is the most prevalent primary glomerulonephritis worldwide, resulting from glomerular deposition of galactose deficient IgA immune complexes. Conventional histological scoring has limited prognostic accuracy, and we lack tools to predict treatment response. To improve disease classification and identify new therapeutics we need better understanding of molecular disease pathways. Integrated glomerular spatial and single nuclei transcriptomic profiling of human renal biopsies may reveal cellular changes and interactions between key cell types including immune infiltrates, mesangial cells and podocytes.

Methods: Renal biopsy cores from IgAN patients and pre-implantation living kidney controls were processed for single-nuclei RNA sequencing (snRNA-Seq). SnRNA-Seq libraries were integrated and analysed using R software to assess cell composition and differentially expressed genes. Formalin-fixed paraffin-embedded (FFPE) renal biopsy sections were profiled via GeoMx for glomerular whole transcriptome, and pilot 10X Xenium experiments using a multi-tissue 377 gene panel, with subsequent analysis of clustering and gene expression using R.

Results: SnRNA-Seq identifies all major renal cell types including tubular, stromal, glomerular, and immune. Podocyte cell numbers are reduced in IgAN relative to mesangial cells, indicating podocyte loss, and immune populations are expanded compared to controls. Gene signatures associated with IgAN include podocyte cell cycling, mesangial Wnt signalling and matrix expansion and immune activation. Spatial analysis supervised by snRNA-Seq revealed heterogeneous glomerular inflammatory and fibrotic patterns, and distribution of NK cells, B cells, T cells and macrophages in the interstitium and around glomerular structures. These observations indicate altered gene pathways associated with immune-glomerular crosstalk in IgAN.

Discussion: Combined single cell and spatial profiling reveals novel cell type specific disease signatures from patient biopsies and highlights cellular crosstalk, and both inter- and intra-sample heterogeneity. we highlight differential immune composition and glomerular podocyte loss. This approach is scalable, and results will be integrated to identify novel therapeutic targets and improve disease stratification and classification.

Lay summary: IgA nephropathy (IgAN) is a chronic kidney disease which results in progressive loss of function, but current treatment is limited to steroids, which at best slow progression. We use new methods to measured changes in gene activity in individual cells, and in tissue context, from healthy and IgAN kidney biopsies performed for clinical indication, creating a detailed map of genes within the kidney tissue. This map reveals differences in the type and location of immune cells and suggests how these immune cells are communicating with the cells of the kidney filtration units in IgAN. Our results provide a blueprint for an approach to better predict how quickly IgAN might progress or respond to treatment in individual patients, and discover new targets for more effective treatments.

Expression of Influenza Neuraminidase Proteins for Vaccine Development and Drug Discovery

Ekta Mukhopadhyay
Rijal Group

Poster

Ekta Mukhopadhyay[1,2], Leiyan Wei [1,2], Alain Townsned [1,2], Pramila Rijal [1,2]

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Abstract

Influenza is a significant health burden with around 1 billion cases globally and an estimated average of 500,000 deaths due to seasonal influenza (WHO, 2025). Influenza virus is prone to mutations and new variants emerge leading to seasonal infections needing timely updated vaccines. There is also a risk of pandemic influenza viruses spill over from animals to humans, so evaluating the protection provided by existing immunity against these emerging viruses is critical. This points towards a pressing need to develop new improved vaccines and anti-viral drugs. So far, major focus has been given to the dominant surface protein haemagglutinin (HA), but limited data is available for second most dominant surface protein- neuraminidase (NA), which is the main interest of our lab. NA induces broader immunity, is less prone to antigenic drift and anti- NA antibodies have been reported to be an independent correlate of protection against influenza. We aim to study NA protein with two approaches: 1) Develop and assess NA based protein vaccine in mice, chicken, pigs and humans, 2) Develop new more effective anti-viral drugs. This work is being undertaken in collaboration with the Pirbright Institute, Structural Biology Laboratory (STRUBI), and Centre for Medicines Discovery (CMD). This work is supported by the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Science (CIFMS), China (grant number: 2018-12M-2-002), Novo Nordisk Foundation and the Townsend-Jeantet Prize Charitable Trust Charity No. 1011770.

Multidimensional Proteomics Methods Reveal the Spatial Architecture of Multicellular GBM Spheroids

Yixin Shi
Fischer Group

Poster

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Abstract

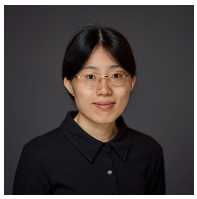
Background: Glioblastoma (GBM) is one of the most aggressive brain tumours and is associated with a poor prognosis. Intratumoral heterogeneity underlies its stemness and therapeutic resistance. However, robust in vitro models to study GBM spatial heterogeneity remain limited, and few studies have explored protein-level alterations in spatial context, an area with strong potential for identifying novel therapeutic targets. To address this, we established a multicellular GBM spheroid model that recapitulates the spatial organisation of human tumours and employed multidimensional proteomics to decode its architecture at the proteome level.

Methods: Spheroids were generated through quad-culture of GBM stem cells (GSCs), iPSC-derived microglia, macrophages, and astrocytes. Single cells and 50-cell clusters from individual cell types were analyzed using a single-cell proteomics (SCP) workflow to generate baseline reference data. On day 5, spheroids were digested layer by layer using Accutase, and single cells from each layer were isolated for SCP analysis via cellenONE. Protein identification was performed using timsTOF Ultra2, and data were processed with DIA-NN (v1.8.1). Downstream bioinformatics analyses were conducted in R/RStudio.

Results: We identified a total of 7,140 proteins across 50-cell and single-cell samples, including markers specific to each cell type. Single-cell proteomics data successfully distinguished cell populations within the spheroids. Spatial dissociation revealed a distinct multi-layered architecture: an outer 'halo' layer composed solely of immune cells, a core enriched in GSCs and astrocytes, and an intermediate zone containing all four cell types with evidence of interaction. Hypoxia analysis showed a progressive increase in hypoxia levels from the halo to the core, indicating a strong spatial correlation with the cellular distribution.

Conclusions: We established a spatially organized, multicellular GBM spheroid model with immune cells enveloping a core of GSCs and astrocytes, and a gradient of decreasing oxygen levels from the periphery to the centre. This model provides insights into the cellular niches within GBM and offers a powerful platform for spatial proteomics-driven discovery of therapeutic targets in tumour microenvironments.

Multiomic Insights into the Pathology of Focal Segmental Glomerulosclerosis



Tianen He
Fischer, Bull, Cornall Labs

Poster

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Abstract

Focal segmental glomerulosclerosis (FSGS) is a poorly understood glomerular disease that leads to kidney failure and frequently recurs post-transplant. We combined spatial renal proteomics and transcriptomics in the Doxorubicin (Adriamycin) nephropathy murine FSGS model, to define pathological glomerular signatures, as an essential first step towards targeted treatments. By analysing the same glomeruli on consecutive kidney sections, with laser capture microdissection coupled to high sensitivity liquid chromatography - mass spectrometry for proteome profiling and Digital Spatial Profiling of transcriptome (NanoString GeoMx), we have characterised >5,000 proteins and >19,000 transcripts from ~100 cells per glomerular region. Both RNA and protein level evidence indicates upregulation of glomerular antigen presentation associated with interferon activity, and highlights druggable targets for further functional validation and therapeutics development. To further deconvolute the pathology in different glomerular cell types, we piloted a single-cell proteomics workflow in immortalised human and murine podocytes, identifying ~1,900 and ~1,000 proteins per cell, showing the feasibility of applying to primary glomerular cells. With immortalised podocytes derived from genetic FSGS patients, we mapped their proteome dynamics during *in vitro* differentiation with a depth of more than 8,000 proteins, revealing pathways involved in diseased podocytes. We are also integrating the proteomic findings with public genomic data associated with renal functions and diseases to validate at another modality. In summary, our research uses multiomic approaches to analyse the FSGS murine model and podocyte cell lines, providing new insights into the glomerular and cellular pathology of FSGS.

Single-Cell Profiling of Spike-Specific B Cells as Immune Correlates of Protection in ChAdOx1 nCoV-19 Vaccinated Individuals

Xiawei Zhang
Lambe Group

Poster

Xiawei Zhang[1], Khiyam Hussain[1], Sagida Bibi[1], Jennifer Alderson[1], Allan Mujati[1], Jinjin Wu[1], Merryn Voysey[1], Dominic Kelly[1], Teresa Lambe[1,2]

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Abstract

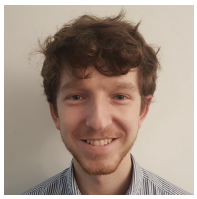
Background: COVID-19 vaccines played an important role in mitigating severe disease during the pandemic. Although the initial urgency has subsided, there remains a need to understand how protection is conferred through understanding the complex immune mechanisms underpinning vaccine response. This knowledge is important particularly due to the ongoing spread of SARS-CoV-2 viral variants, the variable durability of vaccine-induced immunity and the need to optimise long-term immunity. Understanding the immune mechanisms predictive of protection could inform the design and strategic use of next-generation vaccines.

Aim: To identify differences in the B cell receptor (BCR) repertoire using single-cell sequencing between participants who developed breakthrough SARS-CoV-2 infections and those who remained infection-free post-vaccination. To understand how the BCR repertoire can inform understanding of correlates of protection.

Methods: Adult and adolescent peripheral blood mononuclear cells (PBMCs) from post-prime and post-boost samples were obtained in previous randomised efficacy trials (COV001, COV002, and COV006) of the ChAdOx1 nCoV-19 (AZD1222) vaccine, developed by University of Oxford. These were analysed to identify spike-specific BCR repertoires. Cases were defined as individuals who had received at least two vaccine doses prior to a positive PCR test or lateral flow test. Cases were also categorised by the dominant variant at the time of positive test: Wuhan, delta, and omicron. Matched non-case controls were also concurrently assessed. Spike-specific B cells were identified using the Spike dCODE Klickmer® reagent. Antigen-specific B cells and plasmablasts were fluorescence-activated cell sorted (FACS) for downstream single-cell RNA and BCR sequencing using 10x Genomics. Matched bulk BCR-seq data were also obtained for each sample. Statistical analyses were performed to assess BCR repertoires associated with protection against SARS-Cov-2 infection.

Results: A total of 206 participants and 272 samples were included in the single-cell analysis, comprising 83 cases and 123 non-cases. The 83 cases included 20 cases from teenagers and 63 from adults. Of the 83 adult cases, 17 were classified as Wuhan cases, 16 as delta variant cases, and 30 as omicron cases. Antigen specific B cells were successfully identified using dCODE Klickmer® reagent. A total of 193,920 antigen-specific B cells and plasmablasts were included for downstream single-cell analysis. The single-cell analysis is currently ongoing.

The Dominant Impact of Dosing Interval on the Quality of T Cells Induced by SARS-CoV-2 mRNA and Adenoviral Vaccines



Sam M. Murray
Lambe Group

Poster

Sam M. Murray, Ali Amini, Helen Ferry, Lucy C. Garner, Maria Fransiska Pudjohartono, Barbara Kronsteiner, Sagida Bibi, Andrew J. Pollard, Eleanor Barnes, Teresa Lambe, Susanna Dunachie, Paul Klenerman, Nicholas M. Provine**

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3. *Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK*

Abstract

Functional T cell responses are crucial for protective immunity following COVID-19 vaccination, but factors influencing the quality of these responses are poorly understood. Here, we employ an activation induced marker (AIM) assay and single-cell transcriptomic sequencing to analyze SARS-CoV-2 spike-responsive T cells following mild SARS-CoV-2 infection or following one or two doses of mRNA-LNP or adenoviral vectored COVID-19 vaccines, administered at 3-4-week or 8-12-week dosing intervals. Our findings reveal broad functional and clonal T cell heterogeneity in T cells generated by vaccination or infection, including multipledistinct effector populations. T cell function was largely conserved between COVID-19 vaccine platforms but was distinct from T cells generated by SARS-CoV-2 infection. Notably, the dosing interval greatly influenced the quality of T cells after two vaccine doses, particularly after mRNA-LNP vaccination, where a longer interval led to reduced inflammatory signaling and improved secondary proliferation. These insights enhance our understanding of SARS-CoV-2 specific T cells and inform the optimization of mRNA vaccination regimens.

The Frequency and Outcomes of Maternal Cardiac Disease in High-Resource Settings: A Systematic Review and Meta-Analysis

Ling Tao
Marian Knight Group

Poster

Ling Tao, Anshu Ramaiya, Rema Ramakrishnan, Oliver Rivero-Arias, Joris Hemelaar, Marian Knight

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Abstract

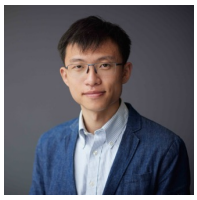
Aims: To estimate the frequency and outcomes of maternal cardiac disease and its subtypes in high-resource settings.

Methods: A systematic literature review was conducted by searching MEDLINE, Embase, CINAHL, and Google Scholar for studies on maternal cardiac disease during pregnancy or up to six weeks postpartum in high-resource settings, published between 1 January 2013 and 8 December 2023. Random-effects meta-analyses were performed, and heterogeneity was assessed.

Results: The systematic review identified 84 studies. The pooled prevalence of maternal cardiac disease during pregnancy or at delivery was 0.54% [95% confidence interval (CI) 0.26%-4.95%, I2=99.5%]. The most prevalent cardiac disease subtypes were arrhythmias [0.68% (95%CI 0.30%-2.84%), I2=99.5%], congenital heart disease [0.21% (95%CI 0.15%-0.57%), I2=98.9%], and valvular heart disease [0.16% (95%CI 0.12%-2.12%), I2=99.9%]. The pooled maternal mortality due to cardiac disease during pregnancy or up to six weeks postpartum was 2 per 100,000 women giving birth (95% CI 2-3 per 100,000, I2=85%). High heterogeneity was the main limitation with different disease definitions and data sources being key sources of variation. 80% of the included data sets came from the United States of America and United Kingdom, limiting the representativeness of the findings for other high-resource settings.

Conclusion: Estimates of the prevalence, incidence, and mortality of maternal cardiac disease and subtypes are available for high-resource settings, although estimates vary between studies, making the true burden uncertain. Further research using consistent disease definitions and comparable data sources is needed. Furthermore, data from a greater diversity of high-income countries are needed.

The Positive and Negative Selection of B Cells Into the Pre-Immune Repertoire



Jianwei Cui
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Poster

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Abstract

The humoral response generated by B cells is critical for immunity, yet the mechanisms governing B cell selection remain incompletely understood. B1a and B1b cells produce antibodies targeting self-antigens and pathogens, contributing to housekeeping functions and immune homeostasis. Their selection strongly depends on self-antigen and BCR signaling early in development.

Using a double-transgenic mouse model expressing intracellular Hen Egg Lysozyme (mHEL KK) to positively select HEL-specific (MD4) B1 cells from fetal liver, we investigated the role of GRB2, antigen-BCR interaction, and timing in B1 cell ontogeny. While this antigen promotes positive selection during fetal development, it causes deletion in adult bone marrow (BM).

In GRB2-deficient mice, we observed increased numbers of B1b cells, marginal zone (MZ) cells, and elevated serum IgM levels. Moreover, B1b cell development was not limited to early ontogeny, highlighting a B cell-intrinsic role for GRB2. GRB2 deficiency resulted in an expanded B1b cell population with broader BCR specificity independent of antigen presence, and antigen exposure further amplified antigen-specific B1b cells by approximately tenfold. Single-cell immune profiling identified a putative B1/MZ precursor population (CD19hiB220lowIgMhiCD43hiCD21hiIgDlow) in adult BM and spleen of GRB2-deficient mice, suggesting developmental linkage between MZ and B1 cells, and indicating a possible maturation trajectory from BM via spleen to the peritoneal cavity. Loss of a GRB2-dependent regulatory pathway controlling IgM receptor levels likely facilitates a shift from negative to positive selection of B cells.

Our findings indicate GRB2 functions as a negative regulator of adult B1b cell development, restricting their formation by influencing the pre-selection cell pool. The positive selection of B1b cells likely involves a two-step process, with GRB2 primarily modulating initial stages. This study provides critical insight into lineage-specific regulation and mechanisms driving positive selection and development of unique B cell populations.

The Role of CD1c in the Pathogenesis of Post-Streptococcal Autoimmune Sequelae

Ching-Chih Wu
Chen Group

Poster

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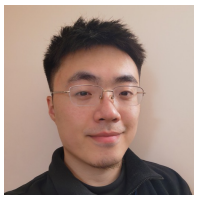
Abstract

Group A Streptococcus (GAS) infection is linked to autoimmune sequelae, causing systemic inflammation in tissues including heart, brain, kidney, skin and joints. Previous studies have revealed that lipids play an indispensable role in autoimmunity which is often associated with dyslipidaemia. However, the underlying mechanism of lipids triggering systemic post-streptococcal autoimmune disorders remains unclear. CD1c is distinct from other CD1 isoforms by its widespread human-tissue expression and upregulation during inflammation and infection. Therefore, we aim to investigate whether CD1c plays a role in the pathogenesis of GAS-driven autoimmune sequelae. Activation of polyclonal T cells obtained from blood of healthy donors was observed in response to GAS infection in a CD1c-dependent manner. Next, CD1c-tetramer+ T cell lines/clones derived from blood or tonsils were expanded and further characterised by functional analysis, exhibiting CD1c specificity. In addition, some CD1c-restricted T cell lines/clones recognised specific lipid antigens showing cross-reactivity towards self- and GAS-derived lipids. Taken together, our results link CD1c pathways to GAS infection, with the potentiate discovery of novel CD1c ligands, which would shed light on the application of CD1c in therapeutic approaches towards autoimmune disorders induced by GAS infection.

USP19 Regulates Adipogenesis and Muscle Wasting in the Development of Sarcopenic Obesity



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Abstract

Background: Sarcopenic obesity (SO) is characterized by the concurrence of excessive body fat accumulation and progressive loss of skeletal muscle mass and function, and has become a global public health concern due to its association with metabolic disorders and geriatric syndromes. USP19 is a membrane-bound deubiquitinase involved in regulating NF□B signaling and eliminating misfolded proteins. Studies have shown that USP19-/- mice exhibit decreased body fat mass and preserve higher muscle mass as compared to wild-type (WT) counterparts. USP19 has also been implicated in muscle wasting in a glucocorticoid- and insulin-dependent manner. This study aims to further investigate the role of USP19 in regulating the homeostasis of adipose tissue and skeletal muscle.

Methods: WT and USP19-/- mice were subjected to a high-fat diet (HFD). Skeletal muscles and adipose tissues were harvested from the mice and analyzed using advanced proteomics and ubiquitomics pipelines. USP19 KO pre-adipocyte cell lines were generated and the lipid accumulation was determined using the BODIPY and Oil Red O staining. Additionally, a panel of USP19-targeting small-molecule inhibitors was synthesized , and inhibitor potency and target cellular engagement was assessed by activity-based protein profiling.

Results: USP19 -/- mice exhibited a leaner phenotype and elevated serum testosterone levels under HFD. Proteomic and ubiquitomic analysis revealed significant alterations in pathways involved in adipogenesis, thermogenesis, and insulin and glucocorticoid signaling. Upon adipogenic differentiation, both USP19 deletion and pharmacological inhibition attenuated lipid droplets formation in mouse preadipocytes in vitro. Furthermore, USP19 inhibition led to elevated protein levels of DCHR24 and AKR1C2, both of which are critical enzymes involved in cholesterol metabolism, potentially affecting glucocorticoid and steroid/testosterone levels.

Conclusions: USP19 serves as a crucial regulator of adipogenesis and steroid hormone metabolism. Our results may highlight the therapeutic potential of USP19 inhibition in obesity-related loss of lean muscle mass (OLLMM), sarcopenia, cachexia and associated disorders.

For Publications or Oral / Poster Presentation:

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