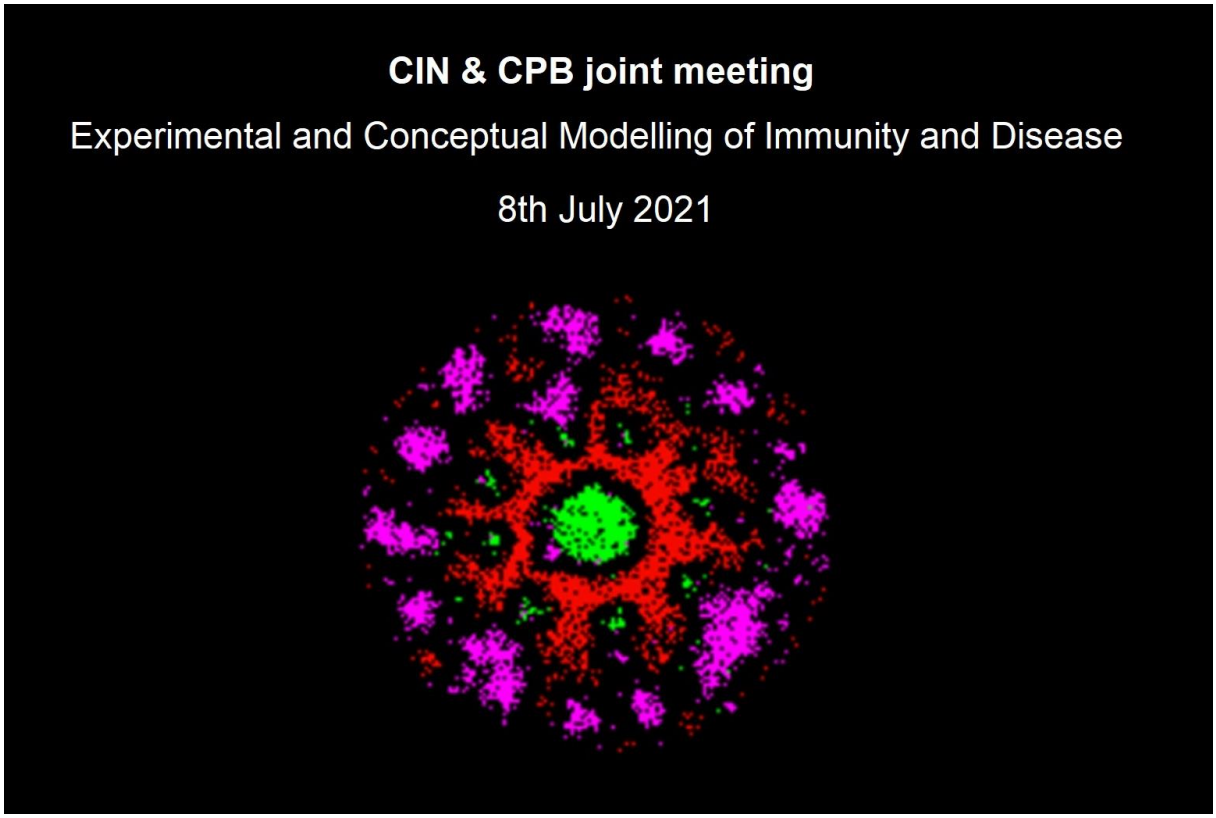

Taking place at the

Jeffrey Cheah Biomedical Centre*

(in-person and online)

Scientific organisers: Clare Bryant and Pietro Cicuta

@Cambridgeimmuno
@camphysbiol
#CPBCIN2021

Any queries please email:

enquiries@immunology.cam.ac.uk or admin@physbiol.cam.ac.uk

*Directions for the Jeffrey Cheah Biomedical Centre (JCBC) can be found on the CIN website: https://www.immunology.cam.ac.uk/directions

CIN & CPB joint meeting:

Experimental and Conceptual Modelling of Immunity and Disease

13:30 Registration

14:00 Opening and Welcome (Professor Clare Bryant)

Session 1: Chair – Professor Clare Bryant

14:05 - 14:50 Keynote Presentation: Professor Michael Dustin

"Modelling phase separation in the immunological synapse"

14:50 - 15:05 Dr James McColl

"Modelling BCR signaling: the importance of stoichiometry"

15:05 - 15:20 Iñigo Ayestaran

"Quantitative dynamics of TCRβ repertoires in healthy individuals"

15:20 - 15:40 Coffee break and posters

Session 2: Chair – Professor Pietro Cicuta

15:45 - 16:00 Dr Amanda Oliver

"Multi-omic spatial mapping of the human lung reveals an IgA B plasma cell survival niche in airway sub-mucosal glands"

16:00 - 16:15 Markus Koerbel

"A Physiological Supported Lipid Bilayer System to Study the First Events in T-Cell Activation"

16:15 - 17:00 Keynote Presentation: Professor Thierry Mora

"Repertoire diversity and dynamics in the immune response"

17:00 - 17:05 Close & acknowledgments

17:05 - 18:00 Drinks reception

Speaker Biographies

Michael L. Dustin

Kennedy Institute of Rheumatology, University of Oxford

Michael Dustin is an Immunologist and Cell Biologist recognized for work on the immunological synapse using the supported lipid bilayers. He also tested this hypothesis *in vivo* using two-photon laser scanning microscopy. Dustin was born and raised in Poughkeepsie, NY. He obtained a B.A. in Biology from Boston University (1984) and a Ph.D. in Cell and Developmental Biology from Harvard University (1990) in the lab of Timothy A. Springer. He was a post-doctoral fellow with Stuart Kornfeld at Washington University School of Medicine and was recruited by Emil Unanue as an Assistant Professor in 1993 and achieved a tenured Associate Professor in 1999. He was recruited by Dan Littman to the Skirball Institute of NYU in 2000 as an Irene Diamond Associate Professor. He was recruited to the University of Oxford by Marc Feldmann in 2013 with a Principal Research Fellowship from Wellcome and the Kennedy Trust for Rheumatology Research, where he is currently a Professor of Molecular Immunology. He was awarded a Presidential Early Career Award in Science and Engineering that supported studies on cell biology of the immune response and is a member of the European Molecular Biology Organization and the National Academy of Sciences.

Thierry Mora

Laboratoire de Physique de l'Ecole Normale Supérieure (LPENS), Paris

Thierry Mora received his PhD in physics at the University Paris-Sud, working on statistical physics approaches to optimization problems. He then moved his interests toward biophysics and neuroscience as a HFSP postdoctoral fellow at Princeton University. Currently he is a CNRS research director at the Ecole Normale Superieure in Paris, working on collective behavior in biological systems, from neuron networks to bird flocks, and on the immune system.

Speaker Abstracts

"Modelling phase separation in the immunological synapse"

Michael L. Dustin

Michael L. Dustin[1], Anastasios Siokis[2], Philippe A. Robert[2], Philippos Demetriou[1], David Depoil[1] and Michael Meyer-Hermann[2,3]

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T cell activation is controlled by the interaction of T cell antigen receptors (TCR) with pMHC complexes in cooperation with adhesion and costimulatory receptors and countered by checkpoint receptors. The final patterning of the immunological synapse is dependent upon physical effects related to molecular size, chemical kinetics and membrane fluctuations combined with active transport and vesicular trafficking processes and current knowledge is outlined here. One of the major adhesion systems is heterophilic interaction of CD2 and CD58 that forms close adhesions (12 nm) over 10-100 μm^2 areas in which the molecules are laterally disordered or "liquid". The other major adhesion pair based on heterophilic interaction of LFA-1 and ICAM-1 transmembrane glycoproteins is actively regulated by mechanical coupling of "extended" LFA-1-ICAM-1 interactions to F-actin through talin to laterally order "solid" clusters. The TCR-pMHC interaction forms persistent clusters that are coupled through soft protein condensates to a F-actin. When T cells interact with a SLB presenting CD58, ICAM-1 and pMHC, a stable immunological synapse forms that can sustains signalling for periods required for T cell activation. The TCR-pMHC and LFA-1-ICAM-1 interactions forms microclusters that trigger an LFA-1 dependent expansion of the contact area and F-actin networks transport both toward the synapse centre. TCR-pMHC enter a central sink (which is irreversible due to ESCRT dependent vesicle formation), while LFA-1-ICAM-1 forms a regenerating adhesion ring. The CD2-CD58 liquid adhesions initially move with TCR-pMHC clusters and move with them toward the centre, but then re-locate to peripheral microdomain. We have previously published agent-based models for the immune synapse. We will discuss how these models can help determine minimal rules for immune synapse organizations than can help guide development of more precise physical descriptions.

"Modelling BCR signaling: the importance of stoichiometry"

James McColl
Postdoctoral Research Associate, Yusuf Hamied Department of Chemistry

James McColl, Martin Wilcock, Joao Ferreira Fernandes, Anna Lippert, Markus Koebel, Gregory Chant, Aleks Ponjavic, Ana Mafalda
Santos, Richard Cornall, David Klenerman and Simon Davis

B cells are key mediators of humoral immunity and rely on signals initiated by the B cell receptor (BCR). The structure of the BCR and mechanism of ligand binding are well characterised, and what remains to be understood is how ligand binding triggers intracellular signalling. A number of opposing models have been proposed. First, the conformation-induced oligomerization model proposes that binding of antigen to monomeric BCR induces a pulling

or twisting force causing conformational changes leading to signalling. Second, the dissociation-activation model proposes that BCRs exist in auto-inhibitory oligomers on the resting B-cell and binding of antigen promotes the dissociation of the BCRs in each cluster, which then are able to signal. Third, the collision coupling model suggests that BCRs are physically kept apart from activating co-receptors or kinases and activation is associated with changes in BCR mobility on the cell surface that then allow for the functional interactions of these elements, again leading to signalling. A final possibility is that encounters with antigen presenting surfaces induce the local, size-based segregation of antagonistic kinases and receptor-type phosphatases, favouring BCR phosphorylation and signalling. The resting state stoichiometry is key for narrowing down the field of potential explanations for BCR triggering. Here we studied the stoichiometry of the BCR in the resting state using total internal reflection fluorescence (TIRF) microscopy and stochastic optical reconstruction microscopy (STORM). Across both live receptor tracking and fixed STORM analysis we obtained no evidence that the BCR forms high-order oligomers in resting cells.

"Quantitative dynamics of TCRβ repertoires in healthy individuals"

Iñigo Ayestaran

PhD student, Department of Oncology

T-cell receptor (TCR) repertoires contain information about past and ongoing immune responses in an individual. While recent advances in TCR sequencing technologies are allowing in depth analysis of repertoire features, most available datasets and methods only focus on static repertoires. In this work, we decided to look at a time series dataset of TCR repertoires in 3 healthy individuals over a span of one year, in order to understand the clonal dynamics of T-cells under no known immune stimuli. We developed a robust statistical framework to identify TCR clones with dynamics that deviate from neutrality. By applying this, we are able to identify large clonal expansion events at multiple time points across all individuals, suggesting distinct immune response events. Finally, we integrate temporal dynamic information of the relevant TCR clones with the amino acid make-up of the corresponding CDR3 region (involved in antigen recognition), to explore the interplay between shared sequence features and similar behaviour over time, which suggests a coordinated immune response to a specific antigen.

"Multi-omic spatial mapping of the human lung reveals an IgA B plasma cell survival niche in airway sub-mucosal glands"

Amanda Oliver

Postdoctoral Research Fellow, Wellcome Sanger Institute

To better understand the cell types and cell-cell interactions of the lung, we generated a multi-omics data set from 5 different locations of the lung: single cell RNAseq, single nuclei RNAseq, VDJseq and Visium 10X spatial transcriptomics analysis. Our analysis has generated 190,000 high quality cell and nuclear transcriptomes with even contribution from trachea, bronchi, bronchioli, upper and lower parenchyma.

Nuclear sequencing and spatial transcriptomics allowed us to identify and map otherwise hard to dissociate cell types that are missing from earlier data sets. We define submucosal gland (SMG) cell populations, comprising mucous, serous, duct and novel myoepithelial cells,

identified only through nuclear sequencing. Using Visium we map all the SMG cell types to distinct locations in the gland, providing orthogonal evidence that these clusters represent distinct cell types. Furthermore, we define a survival niche for IgA secreting plasma cells in the SMG, which includes B cell support from a novel chemokine expressing fibroblast subset. Overall, our work has defined novel cell types in the lung and airways with mapping into the tissue context, including dissection of the micro-anatomy for the sub-mucosal glands and their function. Our approach demonstrates the power of multi-omic integrated spatial datasets for important biological discoveries.

"A Physiological Supported Lipid Bilayer System to Study the First Events in T-Cell Activation"

Markus Koerbel

PhD student, Yusuf Hamied Department of Chemistry

The very first interactions of a T cell with an antigen presenting cell (APC) are key to understanding antigen discrimination in adaptive immunity. T cells need to establish a close contact with the target cell that allows their T-cell receptor to bind the presented antigen. We established a complex supported lipid bilayer (SLB) model of the APC cell membrane to study the influence of adhesion on contact formation and antigen detection. Calcium imaging and TIRF microscopy demonstrated two key findings. First, a fine balance between adhesion and the cellular glycocalyx governs T-cell activation. The adhesion protein CD2 played a dominant role in promoting adhesion and stabilising early contacts. Second, microvilli are necessary to overcome the glycocalyx barrier and define early contact topography. We developed a quantitative image analysis pipeline to characterise four stages of interaction. The T-cell/SLB interface was dominated by dynamics, size-constrained contacts throughout, despite high levels of membrane proximity. Our study highlights the importance of adhesion in regulating T-cell function and we could directly visualize the sequence of events underpinning initial T-cell/target contact. Our findings will be important for better understanding immune diseases and developing immune therapies.

"Repertoire diversity and dynamics in the immune response"

Thierry Mora

Abstract: The immune repertoire responds to a wide variety of pathogenic threats. Immune repertoire sequencing experiments give us insight into the composition of these repertoires. Since the functioning of the repertoire relies on statistical properties, statistical analysis is needed to identify responding clones. Using such methods, I will describe the repertoire level response to the SARS-CoV-2, among other perturbations. More generally, I will show how immune repertoires provide a unique fingerprint reflecting the immune history of individuals, with potential applications in precision medicine.

Notes