COI SCHOLARSHIP DPHIL PROJECT PROPOSALS

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COI Project 1. Characterizing the ultrastructure of coronavirus replication complexes using in-situ cryo-Electron Tomography

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Project Overview

SARS-CoV-2 marked the third zoonotic insertion of a pandemic coronaviral infection into the human population, causing one of the greatest global health challenges to date. As a member of the Coronaviridae family, SARS-CoV-2 is an enveloped virus with a positive non-segmented RNA genome. Viral entry is mediated through the interaction of Spike with ACE2 at the cell surface that triggers the fusion of the viral envelope with the cellular membrane. The viral RNA is released into the cytoplasm where translation of the non-structural proteins from the viral RNA genome induces the formation of the viral replicase complex consisting of interconnected membranous compartments referred to as double-membrane vesicles (DMVs). Assembly of nascent virions occurs in these modified cellular structures derived from components of the endoplasmic reticulum and Golgi complex and new particles egress from assembly structures via exocytosis. A key gap in our knowledge is whether there are distinctions in how different coronaviruses manipulate the cellular ultrastructure to establish replication complexes and productive infection.

Technical advancements in cryo-electron microscopy (cryo-EM) have facilitated high-resolution visualization of macromolecules and pathogens in their native biological settings, including cellular organelles, whole cells, and tissues. Due to limited electron penetration, cryo-focused ion beam combined with scanning electron microscopy (cryo-FIB/SEM) was developed to create 200 nm thick lamellae for high-resolution cryo-electron tomography (cryo-ET). Correlative light and electron microscopy (CLEM) is essential for identifying and targeting regions of interest for cryo-FIB milling and cryo-ET data collection. Cryo-EM imaging of the SARS-CoV-2 life cycle has revealed spatially organized viral replication within dedicated cytoplasmic compartments. Over the past decade, the Oxford Particles Imaging Centre (OPIC) has established a comprehensive pipeline, from sample vitrification to high-resolution cryo-EM and cryo-ET data collection, specializing in live CL3 pathogens, a unique capability in Europe. The Division of Structural Biology has a long history of viral research, including studies on Influenza, RSV, Hantan, Nipah, Dengue, SARS-CoV-2, Rotaviruses, Hepatitis A, B, C & D, EV71, and Noroviruses.

The aim of this project is to explore the fundamental aspects of sub-cellular compartmentalisation of coronaviral infection focusing on the structural composition of the replicase complex. Using the world-leading cryo-EM bio-imaging capabilities of OPIC, this project will answer essential questions surrounding the formation, structure, and spatial organisation of viral replication complexes in a variety of cellular conditions. Recent work in the Wing lab has shown a dynamic interplay between cellular oxygen sensing and coronaviral replication yet, how this affects the formation of replication complexes remains unclear. While this work has shed light on the dynamic relationship between these processes, significant questions remain unanswered. Specifically, the impact of this interaction on the formation of viral replication complexes requires deeper exploration. Future studies should focus on elucidating the mechanisms by which oxygen sensing pathways influence the assembly and function of these complexes. Such insights could potentially reveal novel targets for antiviral therapies and contribute to our understanding of coronaviral pathogenesis.

Disease Relevance

Coronaviruses have emerged as significant pathogens with substantial disease relevance in recent years. These RNA viruses are known for their ability to cause respiratory illnesses in humans and animals, ranging from mild common colds to severe acute respiratory syndromes. The disease relevance of coronaviruses became particularly evident with the emergence of SARS-CoV in 2002, MERS-CoV in 2012, and most notably, SARS-CoV-2 in 2019, which caused the global COVID-19 pandemic. These outbreaks have demonstrated the potential of coronaviruses to cause widespread morbidity and mortality, overwhelm healthcare systems, and disrupt global economies. The zoonotic nature of coronaviruses, allowing them to jump from animal reservoirs to humans, further underscores their importance in public health. Additionally, the ability of coronaviruses to mutate rapidly and potentially evade immune responses poses ongoing challenges for vaccine development and therapeutic interventions, highlighting the critical need for continued research and surveillance in this field.

Key Technology

The key techniques involved in this project include cryo-electron microscopy (cryo-EM), tomography, and molecular virology. Advanced imaging techniques will be employed at the Oxford Particle Imaging Centre (OPIC) to investigate the structural composition and spatial organization of coronaviral replication complexes. Cryo-EM allows for high-resolution visualization of biological structures in their native state, making it an ideal tool for studying the subcellular compartmentalization of viral infection and the formation of replication complexes under various cellular conditions.

Training Opportunities

This project offers training opportunities in:

1) Advanced cryo-electron microscopy techniques at the Oxford Particle Imaging Centre (OPIC)
2) Studying subcellular compartmentalization of coronaviral infection
3) Analysing sthe structural composition of viral replicase complexes
4) Investigating the formation, structure, and spatial organization of viral replication complexes under various cellular conditions
5) Exploring the relationship between cellular oxygen sensing and coronaviral replication
6) Examining the impact of oxygen sensing pathways on the assembly and function of viral replication complexes
7) Developing skills in elucidating mechanisms of viral pathogenesis
8) Potential involvement in identifying novel targets for antiviral therapies

These opportunities will provide hands-on experience with cutting-edge bio-imaging technologies and contribute to the understanding of coronaviral infection processes.

Key Publications

1) Georg Wolff *et al.* A molecular pore spans the double membrane of the coronavirus replication organelle. *Science* (2020).
2) Wing, P.A.C.*, et al.* Hypoxic and pharmacological activation of HIFs inhibits SARS-CoV-2 infection of lung epithelial cells. *Cell Reports* (2021).
3) Staller, E., Carrique, L., Swann, O.C. *et al.* Structures of H5N1 influenza polymerase with ANP32B reveal mechanisms of genome replication and host adaptation. *Nat Commun* **15**, 4123 (2024).
4) Huang, Y., Wang, T., Zhong, L. *et al.* Molecular architecture of coronavirus double-membrane vesicle pore complex. *Nature* **633**, 224–231 (2024).
5) J, Ha ., Sharma, P., Ta, S., et al. 2026. 'Hypoxia Inducible Factors Regulate Pneumovirus Replication by Enhancing Innate Immune Sensing'. *Proceedings of the National Academy of Sciences* 123 (15): e2506647123.

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COI Project 2. Modulating immune responses in cancer and inflammation by rewiring receptor signalling via phosphatase recruitment

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Project Overview

Summary

Signalling through immunoreceptor tyrosine activation motifs (ITAMs) underpins a broad range of immune activation processes, from pathogen defence to allergic inflammation. Aberrant ITAM signalling drives hyperactivation in diseases such as asthma and atopic dermatitis, yet current biologics, including omalizumab, primarily act by neutralising ligands rather than directly regulating receptor phosphorylation. We have developed a new technology, Receptor Inhibition by Phosphatase Recruitment (RIPR), which uses bispecific molecules to recruit surface phosphatases like CD45 in cis to target receptors, effectively silencing tyrosine phosphorylation and rewiring signalling pathways. This project will extend the RIPR concept to ITAM-containing receptors, such as FcεRI, with the goal of directly suppressing activation without blocking receptor-ligand interactions. The work will define how targeted phosphatase recruitment can dampen activation, test the concept in physiologically relevant primary cells, and build translational models to predict the therapeutic potential of RIPR molecules compared with current standards of care.

Background and Rationale

Our group recently demonstrated that RIPR can be used to shut down signalling by inhibitory checkpoint receptors such as PD-1, CTLA-4, and SIRPα, which contain ITIM and ITSM motifs that recruit intracellular phosphatases to attenuate immune responses (Fernandes et al., Nature 2020). By enforcing phosphatase proximity in cis, RIPR bypasses the need for antibody blockade and efficiently silences receptor signalling. This strategy has proven effective in reversing T-cell inhibition and shows promise for therapeutic development across multiple immune checkpoints.

However, while inhibitory receptor signalling can be silenced through ITIM/ITSM dephosphorylation, there are currently no effective strategies to shut down signalling by activatory receptors that signal through ITAM motifs. A prime example is the high-affinity IgE receptor FcεRI, which is expressed on mast cells, basophils, and eosinophils. Engagement of FcεRI by IgE-antigen complexes triggers a powerful activation cascade, driving degranulation and release of histamine, prostaglandins, and cytokines that mediate allergic inflammation and anaphylaxis. Despite its central role in allergy, directly modulating FcεRI signalling has been remarkably difficult. The receptor’s multimeric nature, high surface density, and constitutive association with signalling kinases make it resistant to standard inhibitory approaches. Existing drugs such as omalizumab target free IgE to prevent receptor crosslinking, but do not influence receptor phosphorylation once complexes are formed.

RIPR offers a conceptually new way to tackle this problem by recruiting a phosphatase directly to the activated FcεRI complex, allowing targeted dephosphorylation of ITAM tyrosines and termination of downstream signalling, even after receptor engagement. Extending RIPR to this context would establish a new mechanism to silence activatory receptor pathways and potentially transform the treatment landscape for allergic and inflammatory diseases.

Research Objectives
1. Develop and determine the ability of RIPR molecules to disrupt ITAM-mediated signalling, independent of ligand binding, in engineered cell lines.
2. Confirm that phosphatase recruitment maintains its inhibitory function in primary cells expressing endogenous FcεRI and CD45.
3. Develop translational models to compare the predicted efficacy of RIPR molecules with standard therapies such as omalizumab.

Experimental Approach
The project will begin with the molecular reconstruction of known monoclonal antibodies targeting FcεRI and CD45, using published and patented sequences as templates. These will serve as the building blocks for bispecific RIPR molecules designed to recruit CD45 to the FcεRI complex. The student will then establish engineered reporter cell lines expressing the complete FcεRI complex, allowing quantitative measurement of ITAM phosphorylation and downstream signalling responses using phospho-flow cytometry, calcium imaging, super-resolution imaging and transcriptional reporters.

Once validated in engineered cells, the project will move to primary systems that naturally express FcεRI, for instance, human basophils or mast-cell-like cells derived from haematopoietic progenitors. These assays will provide a physiologically relevant setting to test whether RIPR molecules can suppress, or even reset, the activation triggered by IgE-antigen complexes by targeting FcεRI directly.

Parallel experiments will evaluate how RIPR-mediated inhibition compares mechanistically and quantitatively with omalizumab, which acts by blocking free IgE. By combining experimental data with computational models of receptor occupancy and signal propagation, the project will derive quantitative predictions of efficacy that bridge in vitro biology with translational potential. This integrated approach, spanning molecular design, cell engineering, and modelling, will yield a rich framework to understand and exploit receptor rewiring as a therapeutic principle.

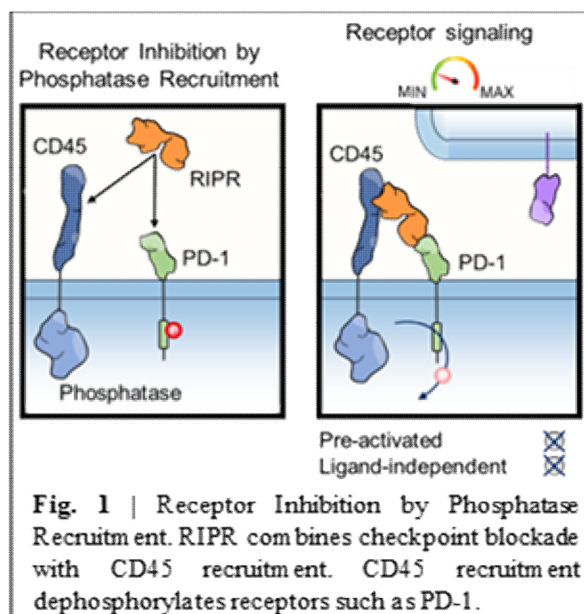

Fig. 1 | Receptor Inhibition by Phosphatase Recruitment. RIPR combines checkpoint blockade with CD45 recruitment. CD45 recruitment dephosphorylates receptors such as PD-1.

Disease Relevance

We expect that the described approach will establish a rapid and facile method to systematically probe the contribution of inhibitory receptors in suppressing T cell effector functions. This information will enable the identification of new targets and guide the development of IR therapeutics in cancer and inflammation. We anticipate the next stage of immunotherapy development to include new molecules that exploit specific aspects of the mechanisms involved in receptor signalling. The RIPR approach may offer a new avenue to directly target receptor phosphorylation and shut down inhibitory receptor signalling with a strong potential for being used to target various surface receptors found in distinct immune cell populations.

Key Technology

Lymphocyte signalling; protein engineering; antibody discovery; biophysical characterization; cell signalling; T cell activation; T cell engineering;

Training Opportunities

This project offers a rare opportunity to work at the interface of protein engineering, quantitative immunology, and translational biology in a close collaboration between academic and industry labs. The student will gain extensive experience in molecular cloning, antibody and bispecific construct design, and recombinant protein production using mammalian expression systems. They will learn to apply biophysical and biochemical tools, such as surface plasmon resonance, ELISA, and flow-based binding assays, to quantify interactions between phosphatases, receptors, and RIPR constructs.

On the cellular side, the student will receive in-depth training in signal transduction analysis, including phospho-protein flow cytometry, calcium flux assays, and cytokine profiling. Work with engineered reporter lines and primary immune cells will build strong competence in cell culture, genome editing, and assay development.

Importantly, the collaboration with DJS will provide exposure to computational and translational modelling, protein engineering, antibody design, and integrating experimental data into predictive frameworks for therapeutic efficacy. This industrial partnership will also offer insights into drug discovery workflows, from molecular design to preclinical validation, and mentoring from both academic and industry leaders in receptor pharmacology and immunomodulation.

By the end of the DPhil, the candidate will have mastered a suite of cutting-edge experimental and analytical techniques, well-positioned to lead future efforts in therapeutic engineering and immune signalling research across academia and biotechnology.

Key Publications

1) Fernandes RA, Su L, Nishiga Y, Ren J, Bhuiyan AM, Ali LR, Majzner R, Ohtsuki S, Rietberg SP, Yang X, Picton L, Savvides CS, Mackall, CL, Sage J, Dougan M, Garcia KC. Immune receptor inhibition through enforced phosphatase recruitment. (2020) Nature, Oct;586(7831):779-784
2) Fernandes RA*, Ganzinger KA*, Tzou J, Jonsson P, Lee SF, Palayret M, Santos AM, Chang VT, Macleod C, Lagerholm BC, Lindsay AE, Dushek O, Tilevik A, Davis SD, Klenerman D. A cell-topography based mechanism for ligand discrimination by the T-cell receptor. (2019) Proc Natl Acad Sci U S A. Jul; 116(28), 14002-14010
3) Chang VT*, Fernandes RA*, Ganzinger KA*, Lee SF*, Siebold C, McColl J, Jönsson P, Palayret M, Harlos K, Coles CH, Jones EY, Lui Y, Huang E, Gilbert RJ, Klenerman D, Aricescu AR, Davis SJ. Initiation of T cell signaling by CD45 segregation at 'close contacts'. (2016) Nat Immunol. May;17(5):574-82

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COI Project 3. Structural Mechanisms of T Cell Receptor Recognition of Peptide Antigen via pMHC Complexes

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Project Overview

Immune surveillance is critical for eliminating cancer cells and cells infected with viruses. Central to this process is the interaction between the T cell receptor (TCR) on T cells and peptide–major histocompatibility complex (pMHC) molecules on target cells. The biochemical and structural features of TCR–pMHC engagement dictate the immune response, yet the fundamental rules governing TCR specificity and sensitivity remain poorly understood.

This project will use cryo-electron microscopy (cryoEM) and structural biology to define the structural “fingerprints” of productive TCR–pMHC interactions that drive T cell activation. We have recently made a key technical breakthrough and determined the first high-resolution structures of native, unmodified TCR–pMHC complexes from SARS-CoV2–infected individuals, despite their low affinity and conformational flexibility. This advance establishes a robust cryoEM pipeline to characterize native TCRs—tumour-reactive or pathogen-specific—in complex with natural pMHCs.

We will compare diverse complexes to identify conserved features and structural variations linked to specificity, sensitivity, and affinity using recombinant protein complexes. We will further advance this work to native TCR/CD3–pMHC assemblies in the context of membranes, as formed within the immunological synapse, using in situ cryo-electron tomography.

These studies will uncover the molecular basis of TCR recognition and provide critical insights for selecting TCRs with optimal specificity and safety for TCR-based immunotherapies.

Disease Relevance

- Virus infections
- Cancer
- Autoimmune diseases

Key Technology

- Molecular biology
- Protein biochemistry
- cryoEM single particle analysis
- cryo-electron tomography
- in situ structural biology
- cryoFIB/SEM lamella preparation
- Correlative fleorescence and electron microscopt

Training Opportunities

We are located in the Division of Structural Biology, Wellcome Trust Centre for Human Genetics, which provides an ideal environment for multidisciplinary and integrative studies. We also have regular access to eBIC at Diamond Light Source for data collection and computation. Individual projects are tailored to particular student's interests and cover techniques in molecular, cellular and structural biology. Through the projects, students will be trained in

- Molecular cloning, protein expression and protein purification
- Protein biochemical/biophysical characterization
- CryoEM single particle structure determination and /or
- Cryo-electron tomography and sub-tomogram averaging
- Correlative light and cryoEM imaging of virus infection
- Cryo-FIB/SEM lamella preparation and volume imaging
- Data analysis and image reconstruction
- Computer molecular dynamics simulations

Key Publications

1) Hou Z, Shen Y, Fronik S, Shen J, Shi J, Xu J, Chen L, Hardenbrook N, Engelman AN, Aiken C, **Zhang P*** (2025) HIV-1 nuclear import is selective and depends on both capsid elasticity and nuclear pore adaptability. *Nat Microbiol.* 10(8):1868-1885.
2) Akıl C, Xu J, Shen J, **Zhang P*** (2025) Unveiling the structural spectrum of SARS-CoV-2 fusion by in situ cryo-ET. *Nat Commun.* 16(1):5150.
3) Xiang Y, Xu J, McGovern BL, Ranzenigo A, Huang W, Sang Z, Shen J, Diaz-Tapia R, Pham ND, Teunissen AJP, Rodriguez ML, Benjamin J, Taylor DJ, van Leent MMT, White KM, García-Sastre A, **Zhang P***, Shi Y (2024) Adaptive multi-epitope targeting and avidity-enhanced nanobody platform for ultrapotent, durable antiviral therapy. *Cell* 187(24):6966-6980.e23
4) Ma J, Yi G, Ye M, MacGregor-Chatwin C, Sheng Y, Lu Y, Li M, Li Q, Wang D, Gilbert RJC, **Zhang P*** (2024) Open architecture of archaea MCM and dsDNA complexes resolved using monodispersed streptavidin affinity CryoEM. *Nat Commun* 15(1):10304
5) Ni T, Gerard S, Zhao G, Dent K, Ning J, Zhou J, Shi J, Anderson-Daniels J, Li W, Jang S, Engelman AN, Aiken C, **Zhang P*** (2020) Intrinsic curvature of HIV-1 CA hexamer underlies capsid topology and interaction with cyclophilin A. *Nat Struct Mol Biol* **27,** 855–862.

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COI Project 4. Exploring non-canonical ubiquitylation in innate immune pathways

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Project Overview

Introduction: Covalent modification by ubiquitin via Lysine isopeptide bonds is fundamental for regulating protein turnover and function. Additionally, ubiquitin esterification occurs on Serine/Threonine/Tyrosine residues in proteins and on non-proteinaceous substrates including ribose, saccharides, lipids, and small molecule drugs [1,2]. Ubiquitin posttranslational modifications may therefore be much more widespread across cell biological pathways. Recent literature reflects the increased interest in analytical methods for mapping of non-canonical substrates modified by ubiquitin and ubiquitin-like (UBL) proteins [2,3]. We intend to explore non-canonical ubiquitin modifications on proteins and non-protein substrates in the context of innate immune pathways such as interleukin-1beta and type-I interferon signalling.

Experimental approach: Mass spectrometry (MS)-based methodologies involve advanced proteomic techniques to identify ubiquitin modifications on amino acids other than Lysine, such as Serine, Threonine, Tyrosine and Cysteine as well as protein N-termini. After digestion, standard MS workflows identify canonical ubiquitination by detecting a ubiquitin C-terminal tag attached to the amine side chains of Lys residues of substrate-derived peptides suitable for MS/MS sequencing. For non-canonical modifications on proteins and substrates other than proteins, specialized strategies are required, such as using antibodies to enrich N-terminally modified peptides in combination with using high-resolution MS/MS based on softer fragmentation technologies to detect esterification and possibly other types of substrate modifications. We shall explore the application and subsequent optimisation of the UbSite approach [3,4] and also extend this beyond Ubiquitin to ISG15, critical for interferon signalling pathway regulation.

Expected outcomes: Enabling such technologies will reveal a previously unrecognized angle of the ubiquitin code's complexity in cells. In particular, these studies will uncover novel molecular connections between metabolic and innate immune signalling pathways that modulate inflammation linked to type-I interferonopathies and to interleukin-1beta [5].

Disease Relevance

The establishment of profiling non-canonical ubiquitin profiling on protein and non-protein substrates will reveal a previously unrecognized angle of the ubiquitin code's complexity in the modulation of innate immune cells, possibly also B- and T-lymphocytes, relevant to normal physiology, but also in the context of human diseases.

In particular, these studies will uncover novel molecular basis for connections between metabolic and innate immune signalling pathways that control inflammation linked to type-I interferonopathies, immunosurveillance of cancer cells, interleukin-1beta linked autoimmunity, neuroinflammation and ageing.

Key Technology

- Mass spectrometry (MS)-based methodologies including advanced proteomic techniques to identify ubiquitin modifications on amino acids other than Lysine, such as Serine, Threonine, Tyrosine and Cysteine as well as protein N-termini.
- Development of mass spectrometry-based workflow to identify ubiquitinated small molecules, such as lipids, sugars and other metabilites.
- Explore non-canonical ubiquitylation substrate discovery in interleukin-1beta inflammasome activation in cell culture models.
- Explore non-canonical ISG15ylation on non-lysine and non protein substrates. Studying their effects to modulate type-I interferon in cell culture models.

Training Opportunities

- Analytical methods – lipidomics, proteomics, mass spectrometry
- Multi-omics data analysis
- Experimental procedures 1: biochemical enrichment strategies for non-canonical ubiquitylation material from cells
- Cell culture platform
- Transfection methodologies
- Plasmid generation, cloning, molecular biology
- Protein biochemistry, lipid biochemistry
- Metabolomics analysis methods
- Writing skills to prepare scientific publications and doctoral thesis
- Scientific presentation and communication skills

Key Publications

1) Kessler BM. Analytical challenges for mapping non-canonical and non-protein ubiquitin/Ubl modifications by mass spectrometry. Expert Rev Proteomics. 2026 Jan-Feb;23(1-2):13-19. doi: 10.1080/14789450.2026.2624128. Epub 2026 Jan 31. PMID: 41601186.
2) Jochem M, Cobbold SA, Goodman CA, Kueng C, Cerra A, Fielden LF, Kim ML, Schenk P, Agarwal R, Wang XS, Scutts SR, Pandos M, Tang L, Hermanns T, Devine SM, Brzozowski M, Shibata Y, Geoghegan ND, McLean CA, Lechtenberg BC, Hofmann K, Gregorevic P, Komander D. Ubiquitination of glycogen and metabolites in cells and tissues. Nature. 2026 Apr 22. doi: 10.1038/s41586-026-10548-x. Epub ahead of print. PMID: 42020756.
3) Kelsall IR, McCrory EH, Xu Y, Scudamore CL, Nanda SK, Mancebo-Gamella P, Wood NT, Knebel A, Matthews SJ, Cohen P. HOIL-1 ubiquitin ligase activity targets unbranched glucosaccharides and is required to prevent polyglucosan accumulation. EMBO J. 2022 Apr 19;41(8):e109700. doi: 10.15252/embj.2021109700. Epub 2022 Mar 11. PMID: 35274759; PMCID: PMC9016349.
4) McCrory EH, Akimov V, Cohen P, Blagoev B. Identification of ester-linked ubiquitylation sites during TLR7 signalling increases the number of inter-ubiquitin linkages from 8 to 12. Biochem J. 2022 Dec 9;479(23):2419-2431. doi: 10.1042/BCJ20220510. PMID: 36408944; PMCID: PMC9788571.
5) Liang Z, Damianou A, Vendrell I, Jenkins E, Lassen FH, Washer SJ, Grigoriou A, Liu G, Yi G, Lou H, Cao F, Zheng X, Fernandes RA, Dong T, Tate EW, Di Daniel E, Kessler BM. Proximity proteomics reveals UCH-L1 as an essential regulator of NLRP3-mediated IL-1β production in human macrophages and microglia. Cell Rep. 2024 May 28;43(5):114152. doi: 10.1016/j.celrep.2024.114152. Epub 2024 Apr 25. PMID: 38669140

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COI Project 5. Lipid specific pathway in malignancy and development of novel therapeutics

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Project Overview

Targeting T-cell responses represents an emerging strategy for modulating immune responses in cancer. While much of cancer immunology has focused on peptide antigens presented by classical MHC molecules, alternative antigen-presentation systems are increasingly recognised as important contributors to tumour–immune interactions. Among these, the CD1 family of non-polymorphic, MHC-like molecules presents lipid antigens to T cells, offering a distinct and potentially underexplored axis for immune recognition and therapeutic intervention.
Malignant transformation is associated with substantial alterations in cellular metabolism and membrane lipid composition. These changes may influence the repertoire of lipids available for presentation, potentially altering lipid-reactive T-cell function and contributing to immune evasion. In addition, tumour-intrinsic and microenvironmental factors may shape antigen presentation and T-cell activation states, further influencing disease progression and response to therapy. This project aims to explore how tumour-associated lipid pathway changes influence T-cell responses, with the goal of identifying new targets for therapeutic benefit.
To address this, the project will incorporate bioinformatic and lipid profiling approaches to define disease-associated lipid landscapes and their perturbation during malignancy. Integration of in vitro and in vivo cellular and molecular immunology will enable the identification of candidate antigenic lipids, characterisation of CD1-dependent presentation pathways, and mapping of T-cell responses linked to these signals in malignancy. These combined approaches will broaden our understanding of how lipid antigen presentation contributes to tumour immunity and how this can be deployed for development of novel therapeutic strategies.

Disease Relevance

Immune dysregulation is a defining feature of many human diseases, including cancer. T cells play critical roles in tumour surveillance and immune control, yet cancers frequently evade or reshape immune responses, limiting the effectiveness of existing immunotherapies. Understanding how antigen recognition pathways operate in malignant settings is therefore central to improving disease outcomes. Lipid antigen presentation represents a relatively underexplored dimension of tumour–immune interactions. Altered cellular metabolism, a hallmark of malignancy, can profoundly change lipid composition and antigen-presentation pathways within tumour cells and the surrounding microenvironment. These changes may influence the activation or suppression of lipid-reactive T cells, contributing to immune evasion.

Key Technology

This project will employ a suite of well-established and emerging technologies in human immunology enable direct analysis of immune cells from human blood and tissues. Core experimental platforms include functional T-cell assays, allowing assessment of antigen recognition and effector responses. Where appropriate, human organoid or in vivo models will be used to capture elements of the tissue and tumour microenvironment. The project will make extensive use of multiparameter flow cytometry, mass cytometry, and high-dimensional immune profiling technologies to enable detailed characterisation of disease-associated immune signatures.

Training Opportunities

The student will be mentored by supervisor team, benefiting from complementary expertise in human immunology, antigen presentation, and translational research. They will be fully integrated into the research group and will participate in regular lab meetings, journal clubs, seminars, and institute-wide scientific activities across the CAMS Oxford Institute and the wider Oxford research environment.

The project will provide hands-on training in experimental immunology and data analysis, alongside opportunities to develop skills in study design, critical evaluation of scientific literature, and collaborative research. The student will be encouraged to contribute to manuscript preparation and scientific presentations, supporting the development of academic writing and communication skills.

In addition to project-specific mentoring, the student will have access to the Medical Sciences Division Skills Training Programme, which offers a comprehensive portfolio of courses covering core areas of researcher development. Students are actively encouraged to make full use of these training opportunities to support their academic and professional development throughout the DPhil.

Key Publications

1) Cao, T.P. et al. Sideways lipid presentation by the antigen-presenting molecule CD1c. Nat Commun 17, 998 (2025).
2) Huang, S. et al. CD1 lipidomes reveal lipid-binding motifs and size-based antigen-display mechanisms. Cell 186, 4583-4596 e4513 (2023).
3) Cao, T.P. et al. A structural perspective of how T cell receptors recognize the CD1 family of lipid antigen-presenting molecules. J Biol Chem 300, 107511 (2024).
4) Chen, Y.L. et al. Group A Streptococcus induces CD1a-autoreactive T cells and promotes psoriatic inflammation. Sci Immunol 8, eadd9232 (2023).
5) Hardman, C.S. et al. CD1a promotes systemic manifestations of skin inflammation. Nat Commun 13, 7535 (2022).

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COI Project 6. Characterising tumour-reactive T cells in lung cancer patients undergoing immune checkpoint inhibitor therapy

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Project Overview

Lung cancer remains one of the leading causes of cancer-related mortality worldwide. Despite recent advances, including the use of immune checkpoint inhibitors (ICIs), only a subset of patients achieves durable responses, and predictive biomarkers of benefit remain limited. Tumour-reactive T cells—lymphocytes that specifically recognize and tumour antigens and kill the tumour cells—play a pivotal role in mediating the effectiveness of immunotherapy. However, their phenotypic and functional characteristics in cancer micro-environment, how they interact with cancer cells and other cells in the micro-environment and how these are modulated by ICI treatment are largely unknown. Understanding the biology of these cells may uncover novel biomarkers and therapeutic strategies to improve patient outcomes.

In this study, we aim to characterise tumour-reactive T cells in a cohort of lung cancer patients receiving immune checkpoint inhibitors and to investigate how these cells shaped by therapy. Making use the well-established pipelines in our Lab, in particular linking the antigen specific T cell in tissue. We will profile the phenotype, clonality, functional state, and tumour specificity of circulating and tumor-infiltrating T cells before and after treatment, and correlate these features with clinical outcomes (response, progression-free survival, overall survival) to identify biomarkers of benefit and mechanisms of resistance.

Disease Relevance

This study is directly relevant to improving outcomes for lung cancer patients because it seeks to identify clinically actionable immune biomarkers associated with treatment benefit and resistance. By characterising tumour-reactive T cells in both blood and tumour tissue before and after ICI therapy, the project may enable more precise prediction of patient responses, inform treatment selection, and guide the development of next-generation immunotherapeutic strategies. Ultimately, these findings could contribute to more personalised and effective approaches to lung cancer treatment, improving survival and quality of life for patients.

Key Technology

Sing-cell multi-Omics technology including sc-RNASeq/TCRSeq,
Spatial multi-Omics technology including spatial gene-expression/TCRseq,
High dimensional Flow cytometry
in vitro tumor-reactive T cell isolation and expansion,
bioinformatic data analysis

Training Opportunities

The student will receive hands-on training in processing human tumor tissues, primary cell culture, and multiparameter flow cytometry with FACS to isolate rare T cell populations. They will learn workflows of single-cell RNA and TCR sequencing, and how to integrate single-cell phenotype with TCR clonotype and repertoire analysis. The student will present at lab meetings, and engage with clinical collaborators, building a versatile skill set in translational cancer immunology.

Key Publications

1) Pinho, M.P.; et al. Characterization of tumor-specific CD8 T cells in HR+ breast cancer reveals an impaired antitumoral response in patients with lymph node metastasis. Cell Reports Medicine, 6:8, 102252. (2025)
2) Hamid MHBA., et al. Unconventional human CD61 pairing with CD103 promotes TCR signaling and antigen-specific T cell cytotoxicity. Nat Immunol 25, 834–846 (2024).
3) Liu G. et al. Long-persisting SARS-CoV-2 spike-specific CD4(+) T cells associated with mild disease and increased cytotoxicity post COVID-19. Nat Commun 16:8743 (2025)
4) Peng Y., et al. An immunodominant NP105-113-B*07:02 cytotoxic T cell response controls viral replication and is associated with less severe COVID-19 disease. Nat Immunol 23:50-619 (2022).
5) Abd Hamid M. et al. Self-Maintaining CD103(+) Cancer-Specific T Cells Are Highly Energetic with Rapid Cytotoxic and Effector Responses. Cancer Immunol Res 8:203-216 (2020)

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